

Annual Report

July 1, 2025 - June 30, 2026

and

27th Annual Scientific Conference

September 17, 2026

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A Personal Note

After 28 years as Director of the Arizona Alzheimer's Consortium, I am stepping down from this role (and from my longstanding position at the Banner Alzheimer's Institutes) to deepen my focus on Alzheimer's prevention and spend more time with my family. I am excited about this next chapter in my professional and personal life, the impact I hope to have, and the chance to continue to work with and support many of you in my more time-limited, independent but affiliated roles.

I am thrilled to announce that our colleague Jessica Langbaum, PhD, will become the Consortium's next Director. Her appointment was made after full approval from the Consortium's Board of Directors and Internal Scientific Advisory Committee. As many of you know, Jessica is an international leader in Alzheimer's prevention research, the disclosure of genetic and biomarker risk factors, and the science of research engagement. Since becoming Director of the NIA-sponsored Arizona Alzheimer's Disease Research Center (ADRC) in July 2024, she has done a masterful job overseeing and bringing new vitality to this well-known center, and spearheading the effort to submit a strong competitive renewal grant. Thanks to Jessica and the other ADRC Core and REC leaders, the ADRC recently received a notification of award for this $22.5M five-year renewal grant. Jessica is well known to many of you for her collaborative and interpersonal skills, her passion for our shared goals, and a genuine interest in supporting the interests and efforts of our colleagues and collaborators. Please join me in welcoming Jessica in her new role, thanking her for taking on this additional responsibility, and congratulating the ADRC team for its successful grant application.

Earlier this year, David Jerman stepped down from his role as the Consortium's Administrative Director to spend more time with his family. As many of you also know, David has worked closely with me in this administrative role from the start of the Consortium in 1998, and he has been critical to its shining success. In addition to how he actively supported colleagues from each of our organizations, he fostered close working relationships with Arizona's elected and Department of Health Services officials, underscored our reputation for scientific and fiscal accountability, productivity and impact, and loved the work that you do.

I am delighted to note that Winnie Liang, PhD, became the Consortium's Administrative Director this past January. Many of you know Winnie for her prior contributions to AD transcriptomics research, and next-generation sequencing and research operations at TGen. Some of you also know about her care and attention to details when it comes to the Consortium's Annual Reports, Conferences, and grant reviews. Before becoming the Consortium's Administrative Director, she worked closely with David to learn about the role, worked with the Consortium's finance, audit and legal colleagues, and received unanimous approval to become the Consortium's Administrative Director. In addition to her role as the Consortium's Administrative Director, she is the ADRC's Administrative Director, working closely with Jessica and the other ADRC Core and REC leaders.

I could not be more grateful for everything that you, our colleagues, collaborators, supporters and valued research participants have done to accomplish so much, achieve extraordinary goals, give us a chance to transform the fight against Alzheimer's and related diseases, and establish a statewide model of research that makes it possible to do things together that none of us would be able to do on our own.

I have always viewed leadership transitions as an opportunity to underscore valued goals, find ways to address problems in new and important ways, and galvanize interest, excitement and efforts to accomplish those goals. The Consortium has the right successors in place, and it has a growing number of researchers, clinicians, and leaders needed to accomplish some of our longstanding goals, consider new opportunities and reach for the stars.

To be successful, we will need to maintain the right collaborative spirit—not just be nice to each other but to proceed with a hunger to capitalize on complementary resources and strengths to achieve the impossible. We will need to remain courageous and bold, avoid complacency, and take informed risks when needed. We will need to create the kind of environment in our organizations and around the state that attracts the best and brightest people, fosters their career development, and allows them to recognize that Arizona is the place to make their dreams come true.

From the beginning we have proposed some breathtaking goals, which include the idea of finding and supporting access to the first effective Alzheimer's prevention therapies and working to make Alzheimer's a distant memory sooner than most people think. Thanks to your efforts, it may be possible to find the first effective prevention therapy in unimpaired people with a positive Alzheimer's blood test within a year and set the stage to find treatments that dramatically, if not completely, prevent the onset of AD in those with a negative blood test a few years after that. While I cannot guarantee the timeline, I remain confident that we are on the right track in this and other endeavors because of you.

While I am stepping down from my administrative leadership roles, I am excited about the chance to have more time with my family, and am also excited to continue being a part of the Arizona Alzheimer's Consortium and seeing what you are able to do, working together, in the fight against Alzheimer's and related diseases.

With deepest gratitude,



Eric M. Reiman, MD

Founding Director of the Arizona Alzheimer's Consortium

Introduction to the Annual Report

We are pleased to welcome you to our 27th Annual Scientific Conference, which will again reflect the continued progress, productivity, and growth of the Arizona Alzheimer's Consortium, the NIH-sponsored Arizona Alzheimer's Disease Research Center (ADRC), and our participating organizations, the pioneering contributions and leadership roles of our scientific and clinical leaders, and the unprecedented opportunity that we and others in the field have to transform the fight against Alzheimer's and related diseases (AD/ADRD). This year's conference, which is sponsored by the University of Arizona and will be held in Tucson, is expected to include well over 400 participants and 230 scientific abstracts and presentations. We are thrilled to have Reisa Sperling, MD, Professor of Neurology at Harvard Medical School, Director of the Center for Alzheimer's Research and Treatment at the Brigham and Women's Hospital and Massachusetts General Hospital, and a dynamic leader in Alzheimer's prevention research, will give this year's Leon Thal Memorial Lecture. The lecture honors the memory of Leon Thal, MD, an AD research and drug development leader and longstanding advisor who had a major role in the success of our state-wide Consortium.

Background

The Arizona Alzheimer's Consortium is the nation's leading model of statewide collaboration in AD research. It includes more than 500 researchers, clinicians, and staff from 12 organizations. The Consortium's seven principal institutions include Arizona State University (ASU), Banner Alzheimer's Institute (BAI), Banner Sun Health Research Institute (BSHRI), Barrow Neurological Institute (BNI), Mayo Clinic Arizona, the Translational Genomics Research Institute (TGen), and the University of Arizona (UA). Its five formally affiliated organizations include Banner Alzheimer's Institute-Tucson (BAI-T), the Critical Path Institute (CPATH), Midwestern University, Northern Arizona University (NAU), and the University of Arizona College of Medicine (UA-COM), Phoenix, and it has a close working relationship with the Veterans Administration Health System in Phoenix. Established in 1998, the Consortium is aimed at making a transformational difference in the scientific fight against AD and ADRD, engaging a wide range of communities throughout the state, helping to address the unmet needs of patients and family caregivers, and advancing the understanding and promotion of healthy cognitive aging. The Consortium's major themes include the unusually early detection, study, diagnosis and prevention of AD, the study of brain aging, and investigating the roles of brain imaging and emerging blood biomarkers in these and related endeavors. Its primary goal is to help find the first effective AD prevention therapies as soon as possible, perhaps as soon as next year.

The Consortium is widely recognized as a model of multi-institutional collaboration in biomedical research. It is also recognized for its vision, groundbreaking contributions, productivity, impact, and leadership roles. Its researchers capitalize on expertise and resources from complementary disciplines and organizations to address scientific problems with the greatest possible impact. It receives critical support from the state of Arizona (through the Arizona Department of Health Services [ADHS]), the participating organizations, the National Institute on Aging (NIA)-sponsored Arizona Alzheimer's Disease Research Center (ADRC), and numerous other grants, contracts, and organizational and philanthropic investments.

For the first 28 years of the state and institutionally supported Arizona Alzheimer's Consortium, Eric Reiman, MD, served as its Director. On Oct 1, 2026, Jessica Langbaum will be assuming

that leadership role. For the Consortium's first 27.5 years, David Jerman served as its outstanding Administrative Director. On Jan 10, 2026, Winnie Liang, PhD assumed that administrative leadership role. Carol Barnes has chaired its 26-member Internal Scientific Advisory Committee (ISAC) since 1999, and leading officials from each of the Consortium's principal organizations serve on the 501(c)(3) organization's Board of Directors.

In addition to their Consortium leadership roles, Dr. Langbaum is also Director of the NIA-sponsored Arizona ADRC and Dr. Liang is its Administrative Director. Dr. Reiman and Alireza Atri, MD, PhD, are its Associate Directors, and Andrea Schmitt is its Grants Director.

The Consortium and ADRC have benefitted from their longstanding external advisors, internationally recognized for their contributions to and leadership roles in AD/ADRD research. Over the years, they have conducted annual site visits, reviewed the progress and productivity of both the Consortium and ADRC, and provided formal feedback and recommendations to researchers, the NIA, and the state of Arizona. Last year, they also provided input and recommendations for the preparation of the ADRC's five year, nearly $22.5M competitive renewal grant application which was submitted in September 2025 and awarded in September 2026.

The Consortium and ADRC are indebted to longstanding external advisors, Marilyn Albert, PhD, Zaven Khachaturian, PhD, Bruce Miller, MD, and Thomas Montine, MD, PhD, as well as our former advisors Leon Thal, MD, Allen Roses, MD, and Richard Frackowiak, MD, PhD, who have had an extraordinary impact on our collaborative model, scientific productivity, and impact. They have set an incredible standard for our new advisors, whom, we are delighted to note, include Joshua Grill, PhD, Allan Levey, MD, PhD, Julie Schneider, MD, Heather Whitson, MD, and David Wolk, MD. All of our advisors have played important leadership roles in the advancement of Alzheimer's research.

The Consortium capitalizes on the state's strengths in brain imaging, emerging blood and other biomarkers, multi-omics, computational, mathematical, statistical, artificial intelligence/machine learning (AI/ML), and other big data analyses of complex data sets, the basic, translational, cognitive, and behavioral neurosciences, and clinical, experimental therapeutics, and neuropathology research. It has made pioneering contributions to the scientific understanding of AD, including the unusually early detection, tracking, study and diagnosis of AD, the accelerated evaluation of putative AD prevention therapies, and the scientific understanding of the aging mind and brain. It has introduced new ways for different stakeholders to work together, provided data, biological samples and interested research participants for researchers inside the state and around the world, and introduced promising cognitive care models for patients and family caregivers. The Consortium continues to attract new researchers and clinicians and support other biomedical research developments in the state, making Arizona a destination center for the advancement of research and care for AD and ADRD.

State and organizational matching funds continue to provide the "glue" needed to promote close working relationships among researchers from different disciplines and different geographically distributed programs, the "fuel" needed to launch new research initiatives, and the "scaffolding" needed to support and advance the Consortium's over-arching goals. Funds are used to support more than eighty research projects each year, almost all of which involve researchers from different scientific disciplines, and about half of which involve different organizations. Arizona is recognized for its courage, its groundbreaking organizational and scientific paradigms, and its ability to make things happen in AD, ADRD and brain aging research.

Shared Resources to Advance the Study of AD

Since securing NIA's first statewide Center grant in 2001, Arizona has received highly competitive, continuous grant funding from the National AD Research Centers (ADRCs) Program and continues to play a prominent role in the national ADRC community. We are delighted to note that

the Arizona ADRC just received notification of its competitive renewal grant from the NIA. In its review, NIA noted the ADRC's thoughtful succession plan, the strengths of its emerging leaders, and its potential to have a major impact in its areas of emphasis. The grant will provide approximately $22.5M in funding over the next five years.

The Arizona ADRC's Administrative, Clinical, Data Management and Statistics, Biomarker, Neuropathology, and Outreach, Recruitment and Engagement Cores, and Research Education Component (REC), provide the leadership, expertise, mentorship, well characterized research participants, biological samples, and privacy-protected data needed to support researchers throughout the state, foster collaborations with colleagues around the world, help establish the next generation of research leaders, and have a profound impact on the fight against AD/ADRD. The ADRC's overarching theme for the 2026-2031 funding period is "blood biomarkers and brain imaging for the early detection, diagnosis, and prevention of Alzheimer's and related disorders," reflecting its leadership role in these areas, and it places a particular emphasis on Arizona adults at the highest AD/ADRD risk.

The ADRC's competitive renewal grant will make it possible to advance the discovery and productive use of blood tests, an area in which Arizona has become an international destination center for the field, continue to develop and use innovative brain imaging techniques and image analysis tools, and leverage resources from Arizona's remarkable brain and body donation program to advance the early detection, tracking, diagnosis, study and potential prevention of AD/ADRD. It will also permit our colleagues to capitalize on the ADRC's shared resources, support their research studies and scientific career development, forge muti-disciplinary multi-institutional collaborations to have the greatest impact, and better address the needs of affected patients and families throughout the state.

The Arizona ADRC has five specific aims: 1) To leverage and extensively share cognitive, clinical, biomarker, and neuropathological data and samples collected in the Clinical, Biomarker, and Neuropathology Cores and managed through the Data Management and Statistics Core for the early detection, tracking, study and prevention of AD/ADRD and to advance innovative research in our growing statewide, multi-institutional collaborative program. 2) To leverage funding from the state of Arizona, Consortium institutions, and philanthropy to expand the Center's research and impact in the early detection, diagnosis, treatment and prevention of AD/ADRD (all Cores and REC). 3) To provide an interdisciplinary environment that attracts, educates, trains, and retains the next generation of AD/ADRD investigators through the REC. 4) To provide extensive outreach and AD/ADRD educational programs for Arizona's communities, and connecting individuals to AD/ADRD research opportunities through the ORE and Clinical Cores. 5) To lead, support, enhance and advance national programs, initiatives, and collaborative programs from the NIA, other ADRCs, and other national and international partners (Administrative Core).

Researchers have capitalized on non-overlapping funds and complementary resources from the Arizona ADRC grant, the Arizona Alzheimer's Consortium, and other NIH, industry, state, organizational and philanthropic grants to provide a more extensive resource of shared data and biological samples for the field than they could from the ADRC alone. For instance, they have generated a resource of blood samples from hundreds of longitudinal assessed research participants who donate their brains and have comprehensive neuropathological assessments after they die. This resource can be used to validate promising new AD/ADRD blood tests that are performed in samples near the end of life and compared to a post-mortem neuropathological standard of truth.

In addition to their other contributions, ADRC and Consortium funds provide data and biological samples needed to confirm the accuracy of blood biomarkers in different members of our community using cerebrospinal fluid (CSF) and brain imaging measurements, setting the stage to dramatically increase the use of these less-invasive tests. They support the study of "preclinical AD" and non-pathological aging in cognitively unimpaired participants who are at differential

genetic risk, including those with and without biomarker evidence of AD, and permit researchers inside Arizona and around the world to incorporate more affordable, scalable, and repeatable blood-biomarkers in independently funded studies.

Productivity, Progress and Impact

The Arizona Alzheimer's Consortium is the leading statewide AD Center in the nation and one of the most productive AD research programs in the world. Since its inception in 1998, its researchers have generated thousands of publications, grants, and contracts and more than $2 billion in new investments. Consortium researchers have made pioneering contributions to the study of AD/ADRD and the aging mind and brain, and they have developed promising research tools to address relevant questions in more impactful ways:

1. In pioneering studies, they continue to help assess genetic and non-genetic (e.g., microbial) risk, resilience, and resistance factors and disease mechanisms, offer targets at which to aim new AD treatments, provide new insights about the pathological changes associated with AD and ADRD, and provide targets for the discovery of drug and gene therapies to treat and prevent AD.

2. They continue to generate invaluable public resources of longitudinal, neuropathological, genetic, transcriptomic, and proteomic data for the field, including an invaluable resource of DNA sequencing, and laser-capture micro-dissected and single nuclei RNA sequencing data from different brain cell types and brain regions that are differentially affected by AD pathology in 100 brain donors with and without AD. Consortium researchers continue to use these and other resources to implicate disease networks, risk factors, and potential drivers at which to aim new AD treatments. To have the greatest possible impact, that have participated in large consortia like the AD Genomics Consortium (ADGC) and Global Neurodegenerative Proteomics Consortium (GNPC), generated complementary (e.g. SomaLogic, ALAMAR and O-link) proteomics platforms to assess those processes involved in the predisposition to, protection from, diagnosis of, and potential treatment and prevention of AD/ADRD with greater power.

3. They continue to introduce new data-sharing, biological sample-sharing, and collaborative paradigms to assist researchers in Arizona and around the world—including data and samples from their own observational studies and prevention trials, data from a growing number of clinical trials of AD and other disorders through the Critical Path for AD (e.g., CPAD, https://c-path.org/programs/cpad/), online memory tests and other information that have been generated in >800,000 participants in the MindCrowd project (www.mindcrowd.org), and the largest resource of privacy-protected longitudinal electronic health record data and biological samples from populations at highest risk for AD/ADRD in the national All of Us Research Program.

4. They and their colleagues have played leadership roles in the early detection and tracking of AD, including the detection and tracking of progressive brain imaging, other biomarkers, and cognitive changes—as well as the detection of neurodevelopmental changes in cognitively unimpaired persons at different levels of genetic risk based on their six common APOE genotypes They have introduced new research paradigms, image-analysis techniques, and other approaches to help in this endeavor. Their work originally anticipated and subsequently advanced the conceptualization of preclinical AD.

5. They have worked with their Colombian colleagues to establish a registry of about 6,000 persons from the world's largest Autosomal Dominant AD (ADAD) cohort, including nearly 1,200 mutation carriers who are virtually certain to develop AD and become cognitively impaired at the median age of 44, and have conducted pioneering studies of preclinical AD to detect, track and study the earliest stages of Alzheimer's disease. Under the auspices of the Alzheimer's Prevention Initiative (API), they completed the world's first AD prevention trial in this kindred and set the stage for many other prevention trials to follow; they provide an invaluable resource of trial data and biological samples to advance the preclinical study and prevention of AD; and they are about to begin a $75M NIA-supported prevention trial that investigates the ability of an amyloid

plaque-clearing antibody therapy and gamma secretase modulator, alone or in combination, to stave off amyloid plaques and tau tangles after the initial clearance of amyloid plaques.

6. They continue to clarify how different molecular processes and brain cells, regions, networks, and mental operations orchestrate memory and other thinking abilities, and how they are affected by AD and aging. They have developed, tested, and applied groundbreaking neuroscientific, experimental, and behavioral paradigms to help in these endeavors and continue to play leading roles in the study of the aging mind and brain.

7. They have played leadership roles in the development, validation, and impactful and widespread mobile use of brain imaging methods, image-analysis tools and emerging blood biomarkers, the unusually early detection, tracking, study, and diagnosis of AD and the evaluation of AD-modifying and prevention therapies, and have begun to develop and test blood biomarkers for other age-related neurodegenerative diseases (e.g., for TDP43, alpha-synuclein, and cerebrovascular amyloid angiopathy [CAA]) and cerebrovascular disease.

8. They and their collaborators have played leadership roles in the study of chronic traumatic encephalopathy (CTE) through “DIAGNOSE CTE”, an NIH-sponsored longitudinal study which aims to characterize clinical, cognitive, PET, MRI CSF, and blood biomarker, and neuropathological data in National Football League (NFL) players, college football players, and normal control participants who do not significantly participate in contact sports, providing a shared resource of data and biological samples for the field.

9. They continue to provide a world-leading scientific resource of longitudinal and neuropathological data, as well as brain and body tissues for the study of AD, Parkinson’s disease, and ADRD in their Brain and Body Donation Program. They continue to capitalize on the use of emerging biomarkers from living research participants and brain tissue from those who donate their brains after they die to help researchers address their goals with even greater impact.

10. They have established a destination center for the development, impactful study, and widespread use of emerging blood and CSF biomarkers, including potential dried blood and plasma spot tests that require less than a drop of blood.

11. They have characterized cognitive, biomarker, neuropathological, and other effects of COVID-19 infection in living persons and expired brain donors and contribute to the national effort to characterize the long-term brain and body effects of “long COVID” (“post-acute sequelae SARS-CoV-2 infection [PASC]”).

12. As previously noted, the Arizona-led API helped launch a new era in AD prevention research, introduced research paradigms and methods to accelerate the evaluation and potential approval of AD prevention therapies, and has co-led a growing number of other prevention trials. It established precedent-setting public-private partnerships, data and biological sample sharing commitments, and strategies to support the potential development of surrogate biomarker endpoints in the accelerated evaluation and approval of prevention therapies. API continues to provide better tests of the amyloid hypothesis than failed clinical trials in later stages of the disease, extremely large research registries, and APOE gene-matching programs to support interest and enrollment in prevention trials.

13. More recently, API has introduced strategies and fostered discussions among thought leaders in the field to find and support the approval, appropriate and widespread use, coverage and affordability of prevention therapies and the potentially scalable blood tests, cognitive assessments, and biomarker and genetic risk disclosure tools needed to inform their use. As previously noted, it may be possible to find and support the approval and availability of the first effective “secondary AD prevention therapies” in cognitively unimpaired people with Alzheimer’s biomarker changes as early as next year, even better secondary prevention therapies soon after,

and the first effective “primary prevention therapy” in cognitively unimpaired persons without Alzheimer’s biomarker changes after that.

14. Over the years, the Consortium has helped its Arizona researchers establish the nation’s most productive All of Us Research Program, the Precision Aging Network, and its first Clinical and Translational Science Award (CTSA) in conjunction with the University of New Mexico.

15. Consortium researchers continue to develop groundbreaking research methods and strategies, collaborative models and data, and biological sample-sharing paradigms to support these and other research endeavors. They continue to make major contributions to AD research; generate the resources and collaborations needed to recruit and support a growing number of researchers and trainees to our participating institutions, and provide the resources, mentorship, training programs, and grants needed to recruit, retain, and support the research and development of talented colleagues, trainees, and students and develop the next generation of researchers, clinicians and leaders in the fight against AD.

Looking Ahead

As we have noted before, we will continue to reach out to foster collaborations beyond our own disciplines and organizations, foster push-pull relationships between methodological developments and their applications and between basic scientific and clinical research, and develop and extensively share our resources to address important problems in more impactful ways than any of us can do on our own.

We will continue to educate, support, and engage our patients and family caregivers, support the marriage between research and care, treat our valued research participants as partners, and set the stage to provide the best possible care for everyone.

We will continue to play pioneering roles in the unusually early detection, tracking, and study of AD, the discovery of new treatments, the discovery and evaluation of emerging blood tests, the evaluation of AD-modifying, symptomatic, and prevention therapies, and the study and management of brain aging.

We will continue to leverage basic scientific research, multi-omics measurements in the post-mortem human brain, electronic health records and other big data, blood biomarkers and legacy cohorts, and emerging AI tools to advance the discovery of disease mechanisms, investigational treatments and repurposed drugs.

We will continue to support and inform the field’s efforts to develop and test a diversified portfolio of promising drug, antibody, gene-silencing, and gene-editing therapies in the treatment and prevention of AD, including those that may be deployed alone, sequentially or in combination, and the medical and lifestyle interventions that appear to promote cognitive health in other ways in older adults with or without Alzheimer’s biomarker changes.

We will develop representative population-based cumulative risk calculators to inform a person’s short, intermediate and long-term risk of progression to MCI and dementia with or without AD based on a person’s blood biomarker and genetic test results, age, and sex, such that it can be used to inform the appropriate use of effective preventative drug therapies and adherence to lifestyle interventions.

We will continue to help find and support approval of secondary and primary AD prevention therapies as soon as possible, help develop the policies and programs to support the appropriate, widespread, equitable and affordable use of effective prevention therapies and the blood and cognitive tests needed to inform their use, and capitalize on AI technologies to help in these endeavors.

As always, we are extremely grateful to the state of Arizona, NIH, and our participating organizations, our heroic research participants, and all of our other supporters for the chance to make a profound difference in the fight against AD and find effective prevention therapies as soon as possible.

Arizona Alzheimer's Consortium

27th Annual Scientific Conference – Thursday, September 17, 2026

University of Arizona (Host Institution)

Loews Ventana Canyon Resort
7000 N Resort Drive, Tucson, Arizona, 85750

8:00 – 9:00 AM **REGISTRATION, POSTER SET UP, CONTINENTAL BREAKFAST**

9:00 – 9:15AM **WELCOME**

Roberta Diaz Brinton, PhD
Director, Center for Innovation in Brain Science
Regents Professor, Pharmacology, Neurology and Neuroscience
University of Arizona College of Medicine – Tucson

9:15 – 9:40AM **INTRODUCTION**

Eric M. Reiman, MD
Director, Arizona Alzheimer's Consortium

Jessica Langbaum, PhD
Incoming Director, Arizona Alzheimer's Consortium

9:40 – 10:45AM **LEON THAL MEMORIAL LECTURE**
Can we treat Alzheimer's disease a decade before dementia? (And why we must!)

Reisa Sperling, MD
Professor of Neurology, Harvard Medical School
Director, Center for Alzheimer Research and Treatment
Brigham and Women's Hospital and Massachusetts General Hospital

10:45 – 10:50AM **A RESOURCE OF ALZHEIMER'S DISEASE FLUID BIOMARKER EXPERTISE AND ASSAYS FOR RESEARCHERS IN THE ARIZONA ALZHEIMER'S CONSORTIUM**

Nicholas Ashton, PhD
Senior Director, Fluid Biomarker Program
Banner Sun Health Research Institute, Banner Alzheimer's Institute

10:50 – 12:05PM **ORAL RESEARCH PRESENTATIONS – SESSION I**

12:05PM *Student Group Photo*

12:15 – 2:45PM **LUNCH & POSTER SESSIONS**

12:30 – 1:30PM POSTER SESSION I
1:45 – 2:45PM POSTER SESSION II

3:05 – 4:20PM **ORAL RESEARCH PRESENTATIONS – SESSION II**

4:20 – 4:30PM **CLOSING REMARKS**
Eric M. Reiman, MD

Arizona Alzheimer's Consortium
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Oral Research Presentations

SESSION I Moderators: David W. Coon, PhD, & Matthew Huentelman, PhD

10:50 – 11:01 AM **From depression symptom management to dementia prevention: Considering next decade research, treatment, and advocacy priorities to reduce the impact of depression in neurocognitive disorders.** Presenting Author: Jordan Karp, MD. University of Arizona.

11:02 – 11:13 AM **Characterization of cryptic HDGFL2 protein expression in amyotrophic lateral sclerosis compared to healthy controls.** Presenting Author: Sarah Shahub, PhD. Banner Sun Health Research Institute.

11:14 – 11:25 AM **Ambient air concentrations of toxicants and risk of frontotemporal dementia.** Presenting Author: Benjamin Schumacher, PhD, MPH. Barrow Neurological Institute.

11:26 – 11:37 AM **Designing an AI chatbot for older adults with cognitive decline living alone: A qualitative study of user needs and design priorities**. Presenting Author: Abigail Gómez-Morales, PhD, RN. Arizona State University.

11:38 – 11:49 AM **Evaluating polygenic risk scores to predict Alzheimer's and amyloid positive in an electronic health record**. Presenting Author: W. Hudson Robb, PhD. Mayo Clinic Arizona.

11:50 – 12:01 PM **Gut microbiome dysbiosis and PARP1 activation are associated with inflammatory response in the brain and gut in Alzheimer's disease.** Presenting Author: Shabana M. Shaik, PhD. University of Arizona.

Oral Research Presentations

SESSION II Moderators: Lee Ryan, PhD, & Heather Bimonte-Nelson, PhD

3:05 – 3:16 PM **Ultrasensitive immunoassay for plasma eMTBR-243 for tracking tau tangle pathology in Alzheimer's disease.** Presenting Author: Alpana Singh, PhD. Banner Sun Health Research Institute.

3:17 – 3:28 PM **Autism genetic liability in Alzheimer's disease and related neuropathology.** Presenting Author: B. Blair Braden, PhD. Arizona State University.

3:29 – 3:40 PM **Impact of liver dysfunction and transplantation on CNS and inflammatory blood biomarkers.** Presenting Author: Erin E. Greig, BS. Mayo Clinic Arizona.

3:41 – 3:52 PM **Hearing age: A scalable online measure of high-frequency hearing health for aging research within the MindCrowd platform.** Presenting Author: Kanishka Manna, PhD. University of Arizona, College of Medicine-Phoenix.

3:53 – 4:04 PM **Repurposing the FDA-approved A-glucosidase inhibitor Miglitol for Alzheimer's disease: Effects in APOE3/E4 brain organoids and 3xTg-AD mice**. Presenting Author: William Gendron, PhD. Arizona State University.

4:05 – 4:16 PM **A non-inferiority evaluation of digital disclosure: A scalable alternative for returning Alzheimer's genetic and biomarker results.** Presenting Author: Claire Erickson, PhD, MPA. Banner Alzheimer's Institute.

Arizona Alzheimer's Consortium
27th Annual Scientific Conference

Poster Presentations

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1. Acevedo-Molina MC, Wang I, Killion JA, Racette BA, Karway GK. **TOO HOT TO REMEMBER? A SCOPING REVIEW OF CLIMATE HEAT AND ALZHEIMER'S DISEASE AND RELATED DEMENTIAS RISK**. Barrow Neurological Institute; Washington University in St. Louis; Creighton School of Medicine; Arizona Alzheimer's Consortium.

2. Atri T, Denkinger MN, Liu J, Singh A, Surdyn M, Brown V, Martinez G, Kuramoto A, Marques TM, Langbaum JB, Atri A, Ashton NJ. **COMPARING TASSO+ TO VENOUS BLOOD-BIOMARKER LEVELS: A VALIDATION STUDY**. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

3. Bartlett MJ, Erickson RP, Polk FD, Frye F, Doyle KP, Pires PW, Witte MH. **MANUAL LYMPH DRAINAGE IN A MURINE MODEL OF ALZHEIMER'S DISEASE ATTENUATES COGNITIVE IMPAIRMENT AND BIOMARKERS OF DISEASE**. University of Arizona College of Medicine - Tucson; Arizona Alzheimer's Consortium.

4. Becktel D, Frye J, Le E, Whitman S, Doyle K. **HPBCD-MEDIATED LIPID CLEARANCE REDUCES CHRONIC POST-STROKE INFLAMMATION AND PROMOTES IMMUNE RESOLUTION**. University of Arizona; Arizona Alzheimer's Consortium.

5. Bergamino M, Fuentes A, White J, Winslow W, Velazquez R, Stokes A. **FREE-WATER ELIMINATION DIFFUSION MRI DETECTS LONGITUDINAL WHITE MATTER REMODELING IN THE 3XTG-AD MOUSE MODEL**. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.

6. Bernard K, Rautenberg J, Erickson DB, Zollar JN, Pombo EL, Corenblum M, Corenblum J, Hammer M, Hay M, Falk T, Madhavan L. **FURTHER EVALUATION OF PNA5 FOR THE TREATMENT OF COGNITIVE DEFICIT IN A PRE-CLINICAL MODEL OF PARKINSON'S DISEASE.** University of Arizona; Arizona Alzheimer's Consortium.

7. Berry B, Camargo C, Chabrashvili T, Cooper G, Frost N, Giles S, Leahy C, Rosenbloom M, Sabbagh M, Sadowski M, Schreiber C, Schulz P, Soria J, Tousi B, Weisman D, Adams C. **REAL-WORLD LECANEMAB UTILIZATION AND OUTCOMES FROM INITIATION THROUGH MAINTENANCE THERAPY IN EARLY ALZHEIMER'S DISEASE: A MULTICENTER RETROSPECTIVE STUDY (LEADER)**. Minneapolis Clinic of Neurology; University of Miami; SUNY Upstate Medical University; Norton Neuroscience Institute; University of Utah; Memory Treatment Centers; Memorial Healthcare Institute for Neuroscience; University of Washington; Barrow Neurological Institute; NYU Langone Health; Citizens Memorial Hospital; The McGovern Medical School of UTHealth - Houston; The Neuron Clinic; Cleveland Clinic; Abington Neurological Associates; Eisai Inc.; Arizona Alzheimer's Consortium.

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82. Zahra S, Edmonds EC, French SR, Wiskoski HE, Arias JC, Waughman X, Orobiyi E, Vidana P, Escareno CE, Ally M, Johnson K, Mushtaq R, Alexander GE, Rapcsak SZ, Weinkauf CC. **DATA-DRIVEN COGNITIVE CLUSTERS IN A NON-DEMENTED VASCULAR-ENRICHED POPULATION**. University of Arizona; Banner Alzheimer's Institute – Tucson; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

83. Zahra S, Hong AT, Arias JC, French SR, Wiskoski HE, Luu IY, Oxnam EB, Orobiyi EO, Ally M, Escareno CE, Culwell G, Heitkamp E, Vasquez F, Vidana P, Waughman X, Hillis M, Johnson K, Jordan JD, Hishaw GA, Bedrick EJ, Vitali F, Mushtaq R, Altbach M, Pruzin JJ, Huges T, Alexander GE, Tan TW, Weinkauf CC. **HYPERTENSION IS ASSOCIATED WITH BETTER BRAIN HEALTH OUTCOMES IN OLDER-AGE ASYMPTOMATIC CAROTID DISEASE POPULATIONS – A MULTI-COHORT STUDY.** University of Arizona; University of Southern California; Barrow Neurological Institute; Banner University Medical Center – Phoenix; Wake Forest University; Arizona Alzheimer's Consortium.

84. Zhang X, Rastogi A, Hanus S, Dharmendra Mohan Prabu HV, Trivedi MR, Shah J, Chen Y, Readhead BP, Wu T, Su Y, Reiman EM, Wilson MA, Wang Q. **RE-ALIGNMENT OF WGS DATA AND META-ANALYSIS OF MULTIPLE TRAITS IDENTIFIED NOVEL GENETIC RISK LOCI ON THE X CHROMOSOME FOR ALZHEIMER'S DISEASE**. Arizona State University; Banner Alzheimer's Institute; Center for Genomics And Data Science Research, National Human Genome Research Institute, National Institutes of Health; Arizona Alzheimer's Consortium.

85. Zheng K, Dumkrieger G, Chen K, Woodruff B, Baxter L, Caselli RJ, Wang Y, Dumitrascu OM. **RETINAL VASCULAR COMPLEXITY ASYMMETRY AS A POTENTIAL BIOMARKER FOR PRECLINICAL ALZHEIMER'S GENETIC RISK**. Mayo Clinic Arizona; Arizona State University; Arizona Alzheimer's Consortium.

86. Zhu Y, Hsieh CJ, Young A, Sheldon M, Kohli N, Gallagher E, Hou C, Li S, Lee H, Brinton R, Mach RH, McManus MJ. **LIGHTING THE FUSE: ROSTRACE PET MAPS EARLY OXIDATIVE SPARKS THAT PRECEDE ALZHEIMER'S PATHOLOGY**. Children's Hospital of Philadelphia; University of Pennsylvania; University of Arizona; Arizona Alzheimer's Consortium.

87. Atri A, Serrano GE, Beach TG, Denkinger MN, Ashton NJ, Protas HD, Su Y, Sabandal M, Carson R, Spires-Jones T, Finnema S, FNIH SV2A PET Tracer Project Study Team. **[18F]SYNVEST-1 SV2A SYNAPTIC PET CLINICAL-BIOMARKER CHARACTERIZATION IN COGNITIVELY UNIMPAIRED AND EARLY AD/ADRD.** Banner Sun Health Research Institute; Banner Alzheimer's Institute; Massachusetts General Brigham and Harvard Medical School; Biomarkers Consortium in Neuroscience, Foundation for the National Institutes of Health; Yale School of Medicine; University of Edinburgh; Abbvie R&D Discovery Research; Arizona Alzheimer's Consortium.

88. Janarthanam C, Orrú CD, Hughson AG, Holzinger D,Taylor K, Kanthasamy AG, Caughey B, Heym RG, Adler CH, Shill HA, Mehta S, Driver-Dunckley E, Ho AH, Choudhury P, Shprecher DR, Belden CM, Atri A, Zhang N, Chen K, Serrano GE, Beach TG. **MULTISITE STUDY: PREDICTING LEWY BODY DISEASE USING SKIN BIOPSY ALPHA-SYNUCLEIN SEED AMPLIFICATION ASSAYS**. University of Georgia; Laboratory of Neurological Infections and Immunity, Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases (NIAID); AbbVie Deutschland GmbH & Co.; AbbVie Bioresearch Center; Barrow Neurological Institute; Banner Sun Health Research Institute; Mayo Clinic Arizona; Arizona State University; Arizona Alzheimer's Consortium.

89. Orru CD, Beach TG, Adler CH, Shilld HA, Driver-Dunckley E, Mehta SH, Atri A, Lorenzini I, Qiji SH, Intorcia AJ, Hughson AG, Groveman BR, King S, Alam P, Parveen S, Vascellari S, Caugheya B, Serrano GE. **BRAIN-ONLY VERSUS GUT-ONLY A-SYNUCLEINOPATHY: A COMPREHENSIVE AUTOPSY SURVEY WITH BOTH IMMUNOHISTOCHEMISTRY AND SEEDING ASSAYS**. Laboratory Of Neurological Infections and Immunity, Rocky Mountain

Laboratories, National Institute of Allergy and Infectious Diseases (NIAID); Banner Sun Health Research Institute; Mayo Clinic Arizona; Barrow Neurological Institute; University of Cagliari; Arizona Alzheimer's Consortium.

90. Serrano GE, Zhang N, Walker J, Adler CH, Choudhury P, Shill HA, Mehta S, Driver-Dunckley E, Lorenzini I, Qiji SH, Campbell A, Aslam S, McHattie R, Krupp A, Intorcia AJ, Borja CI, Shull A, Wermager ZR, Mariner M, Belden CM, Atri A, Beach TG. **AUTOPSY VALIDATION OF CSF A-SYNUCLEIN SEED AMPLIFICATION DEMONSTRATES ROBUST DETECTION OF LEWY BODY PATHOLOGY AND TYPE 2 PROFILES ASSOCIATED WITH CSF COMPOSITION**. Banner Sun Health Research Institute; Mayo Clinic Arizona; Barrow Neurological Institute; Brigham and Women's Hospital; Harvard Medical School; Arizona Alzheimer's Consortium.

91. Tremblay C, Choudhury P, Driver-Dunckley E, Alasmar Z, Serrano GE, Shill HA, Mehta S, Ho A, Fereshtehnejad SM, Shprecher D, Lorenzini I, Belden CM, Atri A, Adler CH, Beach TG, Dadar M, Zeighami Y. **OLFACTORY DECLINE IN AGING: LONGITUDINAL TRAJECTORIES AND ASSOCIATIONS WITH COGNITIVE DECLINE AND POSTMORTEM NEUROPATHOLOGY**. Douglas Mental Health University Institute; McGill University; Banner Sun Health Research Institute; Mayo Clinic Arizona; Barrow Neurological Institute; University of British Columbia; Karolinska Institutet; Arizona Alzheimer's Consortium.

92. Tremblay C, Freiburghaus T, Pawlik D, Hauer KO, Serrano GE, Zeighami Y, Dadar M, Intorcia AJ, Ossenkoppele R, Pontecorvo MJ, Hansson O, Smith R, Beach TG. **QUANTITATIVE DIGITAL VERSUS SEMI-QUANTITATIVE ASSESSMENTS OF TAU PATHOLOGY IN CORRELATION WITH IN VIVO TAU PET REGIONAL SUVR**. Douglas Mental Health University Institute; McGill University; Banner Sun Health Research Institute; Lund University; Office for Psychiatry and Habilitation, Psychiatric Clinic Lund; Memory Clinic, Skåne University Hospital; Eli Lilly and Company; Vrije Universiteit Amsterdam; Amsterdam Neuroscience, Neurodegeneration; Arizona Alzheimer's Consortium.

Student Poster Presentations

93. Abow Alkhier A, Malek-Ahmadi M, Piras I, Wang Q, Chen K, Devadas V, Luo J, Su Y, Marques T, Denkinger MN, Singh A, Ashton NJ. **INTERACTION OF VEGF GENETIC VARIANTS AND APOE EPSILON 4 ON PLASMA TAU BIOMARKERS IN COGNITIVELY UNIMPAIRED OLDER ADULTS**. Arizona State University; Banner Alzheimer's Institute; Translational Genomics Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

94. Alamb F, Outtena C, Ackerman-Berriera M, Reddy Velmaa G, Pentona C, Reddy Muskua S, Lahamb MS, Ranaa M, Maa N, Thulasingama S, Annaduraia A, Thatchera GRJ. **DISCOVERY OF A "CORRECTOR" VIA HIGH-THROUGHPUT SCREENING TO NEGATE UNWANTED LXR-DRIVEN LIPOGENESIS IN LIVER.** University of Arizona; Arizona Alzheimer's Consortium.

95. Ally M, Bharadwaj PK, Schade RN, O'Shea A, Rayaprolu S, Rodriguez K, Gertler J, Nelson I, Katta S, Huo Z, Habeck CG, DeKosky ST, Woods AJ, Bowers D, Alexander GE. **PLASMA P-TAU217 AND WHITE MATTER HYPERINTENSITY NETWORK PATTERN PREDICTS MEMORY RETENTION IN OLDER ADULTS AT RISK FOR ALZHEIMER'S DISEASE**. University of Arizona; University of Florida; Columbia University; University of Texas at Dallas; Arizona Alzheimer's Consortium.

96. Altekreeti M, Wiskoski H, Ugonna C, Arias J, Trouard T, Weinkauf C. **IMPACT OF ASYMPTOMATIC EXTRACRANIAL CAROTID ARTERY DISEASE ON STRUCTURAL BRAIN CONNECTOME INTEGRITY**. University of Arizona; Arizona Alzheimer's Consortium.

97. Bahrami R, Fleury J, Kim SW. **DIGITAL STORYTELLING FOR CAREGIVER ADAPTATION VIA MEANING-MAKING (DST-CAMM): A THEORY-DRIVEN FRAMEWORK TO SUPPORT DEMENTIA CAREGIVERS' WELL-BEING**. Arizona State University; Arizona Alzheimer's Consortium.

98. Bahrami R, Gómez-Morales A, Kim SW. **DIGITAL STORYTELLING IN DEMENTIA CARE: A SCOPING REVIEW**. Arizona State University; Arizona Alzheimer's Consortium.

99. Bahrami R, Gómez-Morales A, Kim SW. **MEANING-MAKING THROUGH DIGITAL STORYTELLING FOR FAMILY CAREGIVERS OF INDIVIDUALS WITH DEMENTIA**. Arizona State University; Arizona Alzheimer's Consortium.

100. Baiocco L, Nickels K, Lai VT, Kielar A. **PRESERVED METAPHOR COMPREHENSION DESPITE SEVERE LITERAL LANGUAGE IMPAIRMENT IN SEMANTIC VARIANT PPA: EVIDENCE FOR GRADED DEGRADATION OF SEMANTIC KNOWLEDGE.** University of Arizona; Arizona Alzheimer's Consortium.

101. Bantugan MA, Ragsdale S, Kalina A, Vitali F, Wang T, Brinton R. **REVERSE-TRANSLATION OF REAL-WORLD MENOPAUSAL HORMONE THERAPY DATA WITH A HUMANIZED APP/APOE ALZHEIMER'S DISEASE RISK MOUSE MODEL**. University of Arizona; Arizona Alzheimer's Consortium

102. Bartholomew S, Winslow W, Hansen N, Martinez M, Watkins K, Sharma R, Mackler N, Hulme C, Dunckley T, Pirotte P, Velazquez R. **PS19 MICE TREATED WITH THE NOVEL INHIBITOR, DYR533, SHOW ATTENUATED TAU PATHOLOGY, NEUROINFLAMMATION, RNA PROCESSING AND SYNAPTIC FUNCTION**. Arizona State University; Integrated Mass Spectrometry Shared Resources, City of Hope Comprehensive Cancer Center; Translational Genomics Research Institute; University of Arizona; Arizona Alzheimer's Consortium.

103. Belnavis A, Stecher C, Chen K, Chiu S, Ofori E. **MEDICATION NON-ADHERENCE IN COMORBID HYPERTENSION AND DIABETES SELECTIVELY PREDICTS VASCULAR DEMENTIA WITH DISTINCT PERIPHERAL BIOMARKER SIGNATURES**. Arizona State University; Banner Alzheimer's Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

104. Belthur M, Doyle RT, Pastor J, Balasubramanian KS, Verpeut J, Bimonte-Nelson H, Newbern J. **ALTERED BASAL FOREBRAIN-CORTICAL CIRCUIT ACTIVATION FOLLOWING SURGICAL MENOPAUSE IN RATS**. Arizona State University; Arizona Alzheimer's Consortium.

105. Bouchal Shockness SM, Robb WH, Greig EE, Durant A, Castellano T, Zhang M, Seto M, Buckley R, Hohman T, Koran ME. **PARENTAL DEMENTIA HISTORY AND MATERNAL DEMENTIAL ONSET AGE PREDICT AGE OF AMYLOID ONSET IN PROGENY.** Mayo Clinic – Arizona; Mayo Clinic – Rochester; Mayo Clinic – Florida; Vanderbilt Memory and Alzheimer's Center; Massachusetts General Hospital; Arizona Alzheimer's Consortium.

106. Brucato C, Lewis CR, Braden BB, Ofori E. **PTSD, ALLOSTATIC LOAD, & NEURODEGENERATIVE RISK: EVIDENCE FROM THE ALL OF US RESEARCH PROGRAM**. Arizona State University; Arizona Alzheimer's Consortium.

107. Byrne B, Mendoza D, Drake J, Vladimirov V, Schrauwen I. **MIRNA SIGNATURE-MATCHING FOR THERAPEUTIC DISCOVERY IN NEURO-DEGENERATIVE DISORDERS**. University of Arizona College of Medicine – Phoenix; Arizona Alzheimer's Consortium.

108. Bues HF, Keeling EG, McElvogue MM, Ott LR, Bakkar N, Stokes AM. **ADVANCED PERFUSION MAGNETIC RESONANCE IMAGING AND PLASMA BIOMARKERS IN ALZHEIMER'S DISEASE**. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.

109. Carlson R, Williamson N, Howison C, Komlosh M, Basser P, Hutchinson E. **DIFFUSION-WEIGHTED PHASE CONTRAST VELOCIMETRY TECHNIQUE FOR CSF FLOW QUANTIFICATION THROUGH THE RAT CEREBRAL AQUEDUCT**. University of Arizona; National Institute of Health; Arizona Alzheimer's Consortium.

110. Chen C, Chen K. **ENHANCING ALZHEIMER'S DISEASE RESEARCH VIA AI**. Brophy College Preparatory; Arizona State University; Banner Alzheimer's Institute; University of Arizona College of Medicine - Phoenix; Arizona Alzheimer's Consortium.

111. Chen C, Huentelman M, Chen K. **HANDEDNESS AND ALZHEIMER'S DISEASE: RESULTS FROM MINDCROWD STUDY**. Brophy College Preparatory; Translational Genomics Research Institute; University of Arizona College of Medicine - Phoenix; Banner Alzheimer's Institute; Arizona State University; Arizona Alzheimer's Consortium.

112. Chen L, Wiskoski H, Camilo Arias J, Ugonna C, Trouard T, Weinkauf C. **BRAIN MICROSTRUCTURE QUANTIFICATION IN INDIVIDUALS WITH ASYMPTOMATIC EXTRACRANIAL CAROTID ARTERY DISEASE UTILIZING FIXEL-BASED-ANALYSIS OF DMRI**. University of Arizona; Arizona Alzheimer's Consortium.

113. Chen YJ, Chawla MK, Zempare MA, Khattab S, Barnes CA. **ARC MRNA EXPRESSION PATTERN IN CA1 HIPPOCAMPAL SUBREGION REVEALS ENSEMBLE STABILITY DIFFERENCES ACROSS AGE AND COGNITION**. University of Arizona; Arizona Alzheimer's Consortium.

114. Cohen D, Klus J, Espinoza M, Daelemans R, Pfeifer V, Andrews-Hanna J, Mehl M, Grilli M. **LEXICAL FILLERS, APOLIPOPROTEIN E4 STATUS, AND EPISODIC SPECIFICITY IN PAST AND FUTURE AUTOBIOGRAPHICAL THINKING.** University of Arizona; University of Missouri - Kansas City; Arizona Alzheimer's Consortium.

115. Connell B, Wright E, Keiser AA. **INVESTIGATING ACVR1C LOCALIZATION TO THE ENDOSOMAL SYSTEM DURING MEMORY CONSOLIDATION**. Arizona State University; Arizona Alzheimer's Consortium.

116. Crawford D, Leyasi S, Brafman D. **CLONING A PINE-TREE PE-PEGRNA(DT)-SGRNA(DT) VECTOR FOR MODELING THE BIN1 K358R MUTATION**. Arizona State University; Arizona Alzheimer's Consortium.

117. Curley B, Ahanonu E, Toner B, Goerke U, Chen NK, Altbach M, Trouard TP, Bilgin A. **DIFFUSION-WEIGHTED RADIAL TURBO SPIN ECHO FOR HIGH-RESOLUTION DIFFUSION-WEIGHTED IMAGING AT 0.55T.** University of Arizona; Siemens Healthineers; Arizona Alzheimer's Consortium.

118. Das D, Karakay D, Ugonna CP, Matijevic S, Chen NK, Trouard TP, Ryan L, Altbach MI, Bilgin A. **ASSOCIATION BETWEEN BRAIN AGE GAP AND WHITE MATTER HYPERINTENSITY BURDEN IN PRECISION AGING NETWORK**. University of Arizona; Arizona Alzheimer's Consortium.

119. Davis M, Guareña L, Ryan L. **PERCEIVED STRESS AND EPISODIC MEMORY: INVESTIGATING THE MODERATING EFFECT OF PHYSICAL ACTIVITY AMONG HISPANIC AND NON-HISPANIC WHITE MIDDLE AGED TO OLDER ADULTS**. University of Arizona; The Precision Aging Network; The National Institute of Health-National Institute on Aging; The National Science Foundation; Arizona Alzheimer's Consortium.

120. De Louise M, Fermaint M, Valenzuela I, Fang F, Gao H, Luthra M, Intorcia A, Serrano GE, Beach TG, Gundlach A L 5, Schrauwen I, De Ávila C. **TRANSCRIPTIONAL PROFILING OF THE RELAXIN-3/RXFP3 SYSTEM IN ALZHEIMER'S DISEASE AND ANXIETY**. University of Arizona College of Medicine - Phoenix; Indiana University School of Medicine; Banner Sun Health Research Institute; The Florey Institute of Neuroscience And Mental Health; The University of Melbourne; Arizona Alzheimer's Consortium.

121. Dolby AJ, Sonderer CM, Han S, Chen NK. **BACKGROUND SUPPRESSION WITH SIMULTANEOUS CHEMICAL SHIFT ARTIFACT REDUCTION IN ARTERIAL SPIN LABELING**. The University of Arizona; Arizona Alzheimer's Consortium.

122. Dong X, Zhu W, Chen X, Wang H, Li X, Xiong Y, Dumitrascu O, Wang Y. **BRIDGING RESTORATION AND BIOMARKER DISCOVERY: A COMPREHENSIVE FUNDUS IMAGE ENHANCEMENT BENCHMARK FOR RETINAL-BASED ALZHEIMER'S DISEASE DETECTION**. Arizona State University; Clemson University; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

123. Dong X, Zhu W, Xiong Y, Chen X, Wang H, Li X, Dumitrascu O, Wang Y. **VESSEL-AWARE OPTIMAL TRANSPORT FOR RETINAL FUNDUS ENHANCEMENT: PRESERVING MICROVASCULAR BIOMARKERS FOR NON-INVASIVE ALZHEIMER'S DISEASE DETECTION**. Arizona State University; Clemson University; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

124. Dougherty R, Pederson V, Mazurik G, Lovato I, Joshi R, Maillard S, Roemer G, Driscoll A, Bartlett MJ, Cowen SL. **STEREOTYPED MOVEMENTS IMPROVE TIME ESTIMATION IN THE TGF344-AD RAT MODEL OF ALZHEIMER'S DISEASE AND IN HEALTHY RATS**. University of Arizona; Arizona Alzheimer's Consortium.

125. Dumitrascu C, Criste E, Kumar G. **THE LINK BETWEEN PERIODONTAL DISEASE AND NEURODEGENERATION: A META-ANALYSIS OF ASSOCIATION AND THERAPY STUDIES**. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

126. Duncan M, Tallino S, Sandoval I, Manfredsson F, Velazquez R. **AN EXAMINATION OF PATHOLOGY DRIVEN BY TWO HUMAN TAU MUTATIONS ON BASAL FOREBRAIN CIRCUITS AND ANXIETY-LIKE BEHAVIOR IN DOWN SYNDROME TS65DN MICE**. Arizona State University; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

127. French SR, Wiskoski HE, Zahra S, Arias JC, Vitali F, Bedrick EJ, Mushtaq R, Dage JL, Ashton NJ, Pruzin JJ, Rapcsak SZ, Bornhorst JA, Algeciras-Schimnich A, Petersen RC, Reiman EM, Alexander GE, Weinkauf CC, The Health and Aging Brain Study (HABS-HD) Study Team, for The Alzheimer's Disease Neuroimaging Initiative. **RENAL FUNCTION ADJUSTED PTAU217 IMPROVES DIAGNOSTIC PERFORMANCE AND COST EFFICIENCY FOR DETECTION OF AMYLOID PATHOLOGY**. University of Arizona; Barrow Neurological Institute; Indiana University; Banner Alzheimer's Institute; Mayo Clinic Rochester; Arizona Alzheimer's Consortium.

128. Fritz MA, Bhuyian P, Huckabee SL, Keiser AA. **THE RELATIONSHIP BETWEEN HIPPOCAMPAL ACVR1C EXPRESSION, SYNAPTIC DYSFUNCTION, AND SPATIAL MEMORY DECLINE IN HEALTHY AGING**. Arizona State University; Arizona Alzheimer's Consortium.

129. Gallegos S, Zhang Y, Velez Galindo M, Johnson F, Bayouth C, Stein E, Harker S, Braden B. **LONGITUDINAL CORTICAL AGING AND CO-OCCURRING CHALLENGES IN MIDLIFE AND OLDER AUTISTIC ADULTS**. Arizona State University; Arizona Alzheimer's Consortium.

130. Garayzar Lopez A, Oevermann MW, Doyle RT, Diaz Z, Kaur I, Holappa KI, Gonzalez-Cruz I, Hannahs MK, Lizik CR, Bimonte-Nelson HA. **SHAPING MENOPAUSAL MEMORY BY PREGNANCY HISTORY: PARITY-INDUCED COGNITIVE IMPROVEMENTS ARE IMPACTED BY ABSENCE OF FEMALE GYNECOLOGICAL ORGANS**. Arizona State University; Arizona Alzheimer's Consortium.

131. Ginn S, Schofield K, Wilms G, Foley C, Kallabis F, Becker W, Hulme C. **DISCOVERY OF DYR684, A HIGHLY POTENT AND METABOLICALLY STABLE DYRK1A/B DEGRADER**. University of Arizona; University of Bonn; RWTH Aachen University; Arizona Alzheimer's Consortium.

132. Gonzalez AJ, Dorman JL, Olson N, Verpeut J, Conrad C. **DOES A PRIOR HISTORY OR ONGOING CHRONIC STRESSORS EXACERBATE AMYGDALA AND MEDIAL PREFRONTAL CORTEX CREB EXPRESSION IN MIDDLE-AGED VERSUS YOUNG ADULT RATS?** Arizona State University; Arizona Alzheimer's Consortium.

133. Greig EE, Robb WH, Denkinger MN, Bouchal SM, Singh A, Hohman TJ, Dickson R, Jaramillo A, Ashton NJ, Koran MEI. **LIVER DYSFUNCTION INFLATES CIRCULATING PTAU217, HIGHLIGHTING BRAIN DERIVED PTAU217 AS A MORE RELIABLE BIOMARKER**. Mayo Clinic Florida; Mayo Clinic Arizona; Banner Sun Health Research Institute; Vanderbilt University Medical Center; The Sahlgrenska Academy at The University of Gothenburg; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

134. Greig EE, Robb WH, Denkinger MN, Bouchal SM, Singh A, Hohman TJ, Dickson R, Jaramillo A, Ashton NJ, And Koran MEI. **CIRCULATING PROTEINS OF NEURODEGENERATION AND IMMUNE RESPONSE ARE ALTERED WITH LIVER TRANSPLANTATION**. Mayo Clinic Florida; Mayo Clinic Arizona; Banner Sun Health Research Institute; Vanderbilt University Medical Center; The Sahlgrenska Academy at The University of Gothenburg; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

135. Guareña LA, Venkatachalam H, Johnson M, De Both M, Huentelman M, Ryan L, The Precision Aging Network. **PERCEIVED STRESS AND COGNITIVE FUNCTION IN A DIVERSE COHORT: DOMAIN-SPECIFIC ASSOCIATIONS FUNDING.** University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

136. Hanna B, Sierks M. **NOVEL CONFORMATION-SPECIFIC ANTIBODIES ENABLE DETECTION OF FRONTOTEMPORAL DEMENTIA-ASSOCIATED BIOMARKERS IN HUMAN SERUM**. Arizona State University; Arizona Alzheimer's Consortium.

137. Harker SA, Serrano G, Aslam S, Piras IS, Shablin AS, Huentelman MJ, Taguinod F, Braden BB, Lewis CR. **AUTISM GENETIC LIABILITY IN ALZHEIMER'S DISEASE AND RELATED NEUROPATHOLOGY**. Arizona State University; Banner Sun Health Research Institute; Translational Genomics Research Institute; University of Utah; Arizona Alzheimer's Consortium.

138. Hendrickson N, Guareña L, Ryan L. **EARLY RISK, LASTING IMPACT: ADVERSE CHILDHOOD EXPERIENCES AND EXECUTIVE FUNCTIONS IN HISPANIC/LATINO VS. NON-HISPANIC WHITE OLDER ADULTS**. University of Arizona; Arizona Alzheimer's Consortium.

139. Hickey R, Guss P, Huggins A, Flores M, Grilli M, Chou Y-H. **WHITE MATTER CHANGES IN ALZHEIMER'S DISEASE WITHIN A LATIN-AMERICAN POPULATION**. University of Arizona; Arizona Alzheimer's Consortium.

140. Ho G, Matijevic S, Ryan L. **EFFECTS OF EXERCISE ON COGNITIVE PERFORMANCE AMONG OLDER ADULTS**. University of Arizona; Arizona Alzheimer's Consortium.

141. Huckabee SL, Bhuiyan P, Shahub S, Fritz MA, Ashton NJ, Keiser AA. **PSMAD2 DEPENDENT REGULATION OF MOLECULAR AND PLASMA BIOMARKERS IN THE AGING BRAIN**. Arizona State University; Banner Sun Health Research Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

142. Javed A, Pan R. **MEMORY INSPIRED MODELING OF ALZHEIMER DISEASE PROGRESSION USING KNOWLEDGE GRAPH DRIVEN ARTIFICIAL INTELLIGENCE**. Arizona State University; Arizona Alzheimer's Consortium.

143. Kaleeswaran V, Rokey S, Foley C, Bartholomew S, Winslow W, Velazquez R, Dunckley T, Hulme, C. **DEVELOPMENT OF DYR533, A HIGHLY SELECTIVE AND ORALLY BIOAVAILABLE INHIBITOR OF DYRK1A TOWARD THE TREATMENT OF ALZHEIMER'S DISEASE AND/OR DOWN SYNDROME**. University of Arizona; Arizona State University - Banner Neurodegenerative Disease Research Center; Iluminos Therapeutics LLC; Arizona Alzheimer's Consortium.

144. Karakay D, Ugonna CP, Matijevic S, Chen NK, Trouard TP, Ryan L, Altbach MI, Bilgin A. **MICROSTRUCTURAL ALTERATIONS SURROUNDING WHITE MATTER HYPER-INTENSITIES IN THE PRECISION AGING NETWORK COHORT**. University of Arizona; Arizona Alzheimer's Consortium.

145. Karg C, Patrick K, Akamangwa L, Oliver J, Richards R III, Clifford A, Ahmetovic A, David Moses GS, Nural-Guvener H. **ANTIOXIDANT GENE EXPRESSION IN SH-SY5Y CELLS UNDER METABOLIC AND OXIDATIVE STRESS: A QPCR STUDY IN AN ALZHEIMER'S DISEASE MODEL.** Grand Canyon University.

146. Kaur G, Robb WH, Koran ME. **PHENOME-WIDE ASSOCIATION STUDY FRAMEWORK FOR IDENTIFYING CLINICAL CORRELATES OF ALZHEIMER'S DISEASE AND GENETIC RISK IN EHR-LINKED COHORTS.** Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

147. Koyah K, Hughes D, Murzin E, Crook S. **EVALUATING THE IMPACT OF NETWORK SPARSIFICATION ON FUNCTIONAL CONNECTIVITY ANALYSIS IN ALZHEIMER'S DISEASE**. Arizona State University; Arizona Alzheimer's Consortium.

148. Lang S, Mazo L, Vladich Z, Ashton NJ, Holechek S, Tseng H, Klein-Seetharaman J. **BEYOND BPA: BPS EFFECTS ON THE AMYLOIDOGENIC PATHWAY IN DIFFERENTIATED SH-SY5Y NEURONAL CELLS AND THEIR RELATION TO ALZHEIMER'S DISEASE**. Arizona State University; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

149. Lee SM, Hussainy S, Liang J. **DISSECTING THE ROLE OF MITOCHONDRIAL PATHWAYS ON ALZHEIMER'S DISEASE RISK AND RESILIENCE IN THE ROSMAP COHORT**. University of Arizona; Arizona Alzheimer's Consortium.

150. Leinenweber KE, Watkins KL, Mariner BL, Snyder-Mackler N. **SINGLE-NUCLEUS PROFILING OF CELL-TYPE AND AGE-ASSOCIATED RETROTRANSPOSON EXPRESSION IN THE PRIMATE BRAIN**. Arizona State University; Arizona Alzheimer's Consortium.

151. Leyasi S, Hyun F, Brafman D. **GENERATION AND VALIDATION OF ISOGENIC BIN1 KNOCKOUT AND BIN1 P381L HUMAN INDUCED PLURIPOTENT STEM CELL MODELS TO INVESTIGATE ALZHEIMER'S DISEASE RISK MECHANISMS**. Arizona State University; Arizona Alzheimer's Consortium.

152. Li X, Zhu W, Dong X, Wang H, Xiong Y, Dumitrascu O, Wang Y. **NNMOBILENET++: AN EFFICIENT HYBRID CNN-TRANSFORMER FRAMEWORK FOR RETINAL IMAGE ANALYSIS**. Arizona State University; Mayo Clinic Arizona; Clemson University; Arizona Alzheimer's Consortium.

153. Li X, Zhu W, Su Y, Huentelman M, Wang Y, Dumitrascu O. **RETINALGPT: INSTRUCTION-TUNED VISION–LANGUAGE INTELLIGENCE FOR RETINAL BIOMARKERS OF ALZHEIMER'S DISEASE**. Arizona State University; Banner Alzheimer's Institute; Translational Genomics Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

154. Lindemer SL, Felix M, Gomez A, Ashton NJ, Maldonado A, Huentelman M, Chen N, Aguiñaga S, Rodriguez M, Garcia DO. **FEASIBILITY AND ACCEPTABILITY OF AT-HOME PTAU217 COLLECTION USING CAPITAINER® SEP10 DRIED PLASMA SPOT CARDS AMONG MEXICAN-ORIGIN ADULTS**. University of Arizona; Banner Sun Health Research Institute; Translational Genomics Research Institute; University of Illinois Urbana - Champaign; Arizona Alzheimer's Consortium.

155. Lindemer SL, Felix M, Gomez A, Maldonado A, Huentelman M, Chen N, Aguiñaga S, Rodriguez M, Butler D, Garcia DO. **BETWEEN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE AND COGNITIVE FUNCTION AMONG MEXICAN-ORIGIN ADULTS**. University of Arizona; Translational Genomics Research Institute; University of Illinois Urbana - Champaign; Georgetown University; Arizona Alzheimer's Consortium.

156. Lizik CR, Anyigbo KJ, Wu ES, Oevermann MW, Doyle RT, Kalas SA, Garayzar Lopez A, Gonzalez-Cruz I, Hannahs MK, Kaur I, Bimonte-Nelson HA. **THE COGNITIVE EFFECTS OF NONHORMONAL MENOPAUSAL THERAPY DEPEND ON THE PRESENCE OF REPRODUCTIVE TRACT ORGANS: EXPLORING THE NEW HORIZON OF VASOMOTOR THERAPIES**. Arizona State University; Arizona Alzheimer's Consortium.

157. Maillard S, Dougherty R, Pederson V, Roemer G, Sweet E, Cowen SL. **TREADMILL-BASED TASK FOR ASSESSING NEURAL CORRELATES OF TIME ESTIMATION ACROSS MULTIPLE DURATIONS AND CONTEXTS IN THE TGF344-AD RAT MODEL OF ALZHEIMER'S DISEASE**. University of Arizona; Arizona Alzheimer's Consortium.

158. Marshall A, Huggins A, Huynh N, Terner J, Barlis K. **THE IMPACT OF TRAUMA EXPOSURE ON THE RELATIONSHIP BETWEEN COGNITIVE FLEXIBILITY AND EMOTIONAL CLARITY IN OLDER WOMEN**. University of Arizona; Arizona Alzheimer's Consortium.

159. Martin PE, Polk FD, Vikram Aditya R, Cornell T, Pires PW. **INDUCIBLE NITRIC OXIDE SYNTHASE UNDERLIES BKCA CHANNEL DYSFUNCTION AND MICROVASCULAR DEFICITS IN FEMALE 5X-FAD MICE**. University of Arizona; Arizona Alzheimer's Consortium.

160. Massa N, Todd K, Cadiz M, Haug K, Nascari D, Barnett J, Fryer JD. **AGING ALTERS BRAIN RECOVERY TRAJECTORIES FOLLOWING SYSTEMIC ESCHERICHIA COLI INFECTION**. Mayo Clinic Arizona; Translational Genomics Research Institute; Alzheimer's Consortium.

161. Mazo LM, Singh A, Denkinger MN, Liu J, Dieckhoff K, Marques TM, Wilson R, Reyes R, Leuzy A, Ghisays V, Head E, Beach TG, Serrano G, Atri A, Reiman, EM, Langbaum JB, Johnson SC, Ashton NJ. **RELIABILITY OVER SENSITIVITY: COMPARING FULLY AUTOMATED AND ULTRA-SENSITIVE IMMUNOASSAY FOR PTAU217.** Banner Sun Health Research Institute; Arizona State University; University of Wisconsin, Madison; The Michael J Fox Foundation, Gothenburg, Sweden; Banner Alzheimer's Institute; UC Irvine Center for the Neurobiology of Learning and Memory; Arizona Alzheimer's Consortium.

162. McLean JW, Wang T, Brinton RD. **SINGLE-NUCLEI TRANSCRIPTOMICS IDENTIFIES CELL-TYPE-SPECIFIC ESTROGEN-DEPENDENT PATHWAY ALTERATIONS RELEVANT TO ALZHEIMER'S DISEASE IN FEMALE RAT HIPPOCAMPUS**. University of Arizona; Arizona Alzheimer's Consortium.

163. McRobbie-Johnson A, Bernard K, Corenblum MJ, Tonino P, Langlais P, Madhavan L. **PROBING PATHOLOGICAL MECHANISMS IN HUMAN IPSC-DERIVED DOPAMINE NEURONS FROM INDIVIDUALS WITH SPORADIC PARKINSON'S DISEASE**. University of Arizona; Arizona Alzheimer's Consortium.

164. Melick AM, Christiansen K, Krishnan T, Bimonte-Nelson HA, Schaefer SY, Beeman SC, Verpeut JL. **FINE MOTOR IMPAIRMENTS EMERGE PRIOR TO COGNITIVE DYSFUNCTION AND PERSIST THROUGHOUT LIFE IN THE TGF344-AD RAT MODEL OF ALZHEIMER'S DISEASE**. Arizona State University; Arizona Alzheimer's Consortium.

165. Miller B, Rhine K. **NEURONAL AGING REWIRES P-BODIES DYNAMICS**. University of Arizona; Arizona Alzheimer's Consortium.

166. Millmond E, Sutherland S, Ekstrom A, Hill P. **MULTIVARIATE ASSOCIATIONS BETWEEN COGNITION AND GAIT-BALANCE KINEMATICS IN OLDER ADULTS**. University of Arizona; Arizona Alzheimer's Consortium.

167. Moon J, Rajput Y, Judd JM, Keiser AA. **ACVR1C SIGNALING IN THE BASOLATERAL AMYGDALA REGULATES EXTINCTION OF TONE FEAR**. Arizona State University; Arizona Alzheimer's Consortium.

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169. Nascari DG, Beniwal AS, Bouchal SM, Rabichow BE, Eghlimi R, Dufault M, Gibson KA, Grief D, Flick MJ, Alton BD, Parrish FM, Tran I, Williams-Katek AL, Mee ED, Banovich NE, Donev K, Blomquist MR, Fortin Ensign SP, Tran NL, Fryer JD. **CHRONIC GLIAL ACTIVIATION IN ALZHEIMER'S DISEASE DRIVES A TUMOR-SUPPRESSIVE IMMUNE LANDSCAPE.** Mayo Clinic Arizona; Translational Genomics Research Institute; University of California, San Francisco; Arizona Alzheimer's Consortium.

170. Nguyen M, Billingsley K, Brafman D. **GENERATION OF ISOGENIC APOE3[R145C]/4 HIPSC LINE TO MODEL ALZHEIMER'S DISEASE RISK IN AFRICAN ANCESTRY**. Arizona State University; Arizona Alzheimer's Consortium.

171. Nordbeck AJ, Tseng J-H. **DYNAMIC CHANGES IN TAU POST-TRANSLATIONAL MODIFICATIONS DURING HEALTHY AND NEURODEGENERATIVE AGING REVEAL EARLY TAU ALTERATIONS**. Arizona State University; Arizona Alzheimer's Consortium.

172. Norman SL, Liu Y, Green JM, Haaheim LG, Siu HM, Dannhauer M, Chou YH. **INDIVIDUALIZED ELECTRIC FIELD STRENGTH AND MEMORY OUTCOMES FOLLOWING TMS IN MILD COGNITIVE IMPAIRMENT**. University of Arizona; East Carolina University; Arizona Alzheimer's Consortium.

173. Oevermann M, Corbin S, Doyle R, Pastor J, Lizik CR, Wu E, Bimonte-Nelson H. **REMOVED BUT NOT FORGOTTEN: INVESTIGATING THE AGE-DEPENDENT COGNITIVE EFFECTS OF HYSTERECTOMY IN A FEMALE RAT MODEL**. Arizona State University; Arizona Alzheimer's Consortium.

174. Pillutla SVP, Corenblum MJ, Mutha A, Anderson D, Yamamoto M, Madhavan L. **ASSESSING THE EFFECTS OF NRF2 AND E2/P4 LOSS QUIESCENCE-ACTIVATION-SENESCENCE BALANCE OF STEM CELLS IN THE AGING RODENT BRAIN.** University of Arizona; Tohuku University; Arizona Alzheimer's Consortium.

175. Pitea R, Wang V, Li X, Langlais B, Dumitrascu O. **CENTRAL RETINAL VENULAR EQUIVALENT DISCRIMINATES ALZHEIMER'S DISEASE IN UK BIOBANK**. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

176. Puig Rivera VA, Cervantes LJ, Andrews ES, Freveletti D, Grilli MD, Andrews-Hanna JR. **AGING IN CONTEXT: ENHANCED EPISODIC SPECIFICITY AND SOCIOEMOTIONAL CONTENT IN OLDER ADULTS' EVERYDAY AUTOBIOGRAPHICAL THOUGHTS – INSIGHTS FROM THE MIND WINDOW APP.** University of Arizona; Northeastern University; Arizona Alzheimer's Consortium.

177. Pulliam S. **NEURONAL AGING ALTERS STRESS GRANULE MORPHOLOGY AND DYNAMICS IN RESPONSE TO ENVIRONMENTAL AND CELLULAR STRESS**. University of Arizona; Arizona Alzheimer's Consortium.

178. Ragsdale SM, Holmgren G, Vitali F, Brinton RD. **PLASMA PROTEOMIC SIGNATURES OF ALZHEIMER'S DISEASE RISK ARE DIFFERENTIALLY SHAPED BY MENOPAUSAL HORMONE THERAPY FORMULATION, INITIATION TIMING, AND APOE GENOTYPE IN POSTMENOPAUSAL WOMEN.** University of Arizona; Arizona Alzheimer's Consortium.

179. Rausch M, Bhattacharya M. **POSE ESTIMATION AS A BEHAVIORAL SCREENING TOOL FOR FUNCTIONAL GENETIC MODIFIERS OF NEURODEGENERATION.** University of Arizona; Arizona Alzheimer's Consortium.

180. Reed AM, Tomlin KB, Malek-Ahmadi M, Liang WS, Woodruff B, Langbaum JB, Reiman EM, Schaefer SY. **IDENTIFYING NEUROPSYCHOLOGICAL CORRELATES OF A BRIEF PERFORMANCE-BASED TEST OF COGNITION AND DAILY FUNCTIONING IN COGNITIVELY UNIMPAIRED OLDER ADULTS: FINDINGS FROM THE APOE 2.0 COHORT**. Arizona State University; Banner Alzheimer's Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

181. Rich C, Dumitrascu O, Dumkrieger G, Woodruff B, Baxter L, Wang Y, Zheng K. **INTER-EYE DIFFERENCE IN RETINAL VASCULAR TORTUOSITY PREDICTS VERBAL MEMORY.** Mayo Clinic Arizona; Arizona State University; Arizona Alzheimer's Consortium.

182. Rich C, Zheng K, Segovia D, Pitea R, Dumkrieger G, Woodruff B, Dumitrascu O. **RETINAL IMAGING BIOMARKERS OF PRECLINICAL ALZHEIMER'S DISEASE: A SYSTEMATIC REVIEW**. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

183. Richards R III, Clifford A, Ahmetovic A, Bricker S, Conceicao-Larson N, Kay G, Robinson S, David Moses GS, Nural-Guvener H. **CHARACTERIZATION OF OXIDATIVE STRESS AND MITOCHONDRIAL DYSFUNCTION IN AN SH-SY5Y ALZHEIMER'S DISEASE MODEL USING ROS, JC-1, AND PROTEIN QUANTIFICATION ASSAYS**. Grand Canyon University.

184. Roscoe D, Fryer J. **LIFELONG IMMUNE EXPERIENCE DRIVES PHENOTYPIC AND FUNCTIONAL MICROGLIAL CHANGES THAT MITIGATE AMYLOID PATHOLOGY IN MOUSE MODELS OF AD**. Mayo Clinic Arizona; Translational Genomics Research Institute; Alzheimer's Consortium.

185. Sailer A, Rhine K. **AGING-LINKED TDP-43 MISLOCALIZATION DRIVES RNA MISPROCESSING**. University of Arizona; Arizona Alzheimer's Consortium.

186. Sakai A, Rhine K. **AGING-LINKED NUCLEAR PORE DEGRADATION INHIBITS PROPER RNA TRANSPORT AT THE NUCLEUS**. University of Arizona; Arizona Alzheimer's Consortium.

187. Schafernak-Perez LM, Moreno-Rodriguez M, Mufson EJ, Perez SE. **MICROGLIAL HOMEOSTASIS AND WHITE MATTER INTEGRITY IN THE FRONTAL CORTEX OF AGED INDIVIDUALS WITH SUPERIOR COGNITIVE ABILITIES**. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

188. Shakir S, Denkinger MN, Singh A, Liu J, Dieckhoff K, Hanley D, Marques TM, Monuk E, Stark C, Grill J, Reiman EM, Head E, Ashton NJ. **BRAIN DERIVED P-TAU AND PLASMA P-TAU AS BIOMARKERS OF NEUROPATHOLOGY IN ALZHEIMER'S DISEASE: RESULTS FROM AN AUTOPSY COHORT**. Arizona State University; Banner Sun Health Research Institute; University of California Irvine School of Medicine; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

189. Sharma B, Tseng JH. **TAU ACETYLATION DISRUPTS MICROTUBULES HOMEOSTASIS IN ALZHEIMER'S DISEASE MODELS.** Arizona State University; Arizona Alzheimer's Consortium.

190. Sharma G, Rhine K. **THE EFFECTS OF AGING ON TDP-43 MISLOCALIZATION IN HUMAN NEURONS**. University of Arizona; Arizona Alzheimer's Consortium.

191. Shen B, Zheng K, Woodruff B, Caselli R, Chen K, Dumitrascu OM. **ASSOCIATIONS BETWEEN RETINAL VASCULAR MEASURES AND ALZHEIMER'S DISEASE BIOMARKERS**. Cornell University; Arizona State University; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

192. Shiva Prakash S, Pan R. **PREDICTING PERSONALISED COGNITIVE DECLINE TRAJECTORIES IN ALZHEIMER'S DISEASE: A PACE-FPCA FRAMEWORK WITH KNOWLEDGE GRAPH REASONING AND AI AGENT INTERFACE.** Arizona State University; Arizona Alzheimer's Consortium.

193. Shu J, Cheng R, Chen H, Liu L. **DECODING EPIGENETIC HETEROGENEITY IN ALZHEIMER'S DISEASE: DNA METHYLATION SUBGROUPS, PROMOTER BOUNDARY PROTECTION, AND CROSS-TISSUE BIOMARKERS**. Arizona State University; Case Western Reserve University; Arizona Alzheimer's Consortium.

194. Siegel MM, Nenni JA, Beyazyildirim M, Isa AM, Al-Nakkash L. **INFLUENCE OF EXERCISE ON WESTERN DIET INDUCED NEUROLOGICAL AND BEHAVIORAL CHANGES.** Midwestern University; Arizona Alzheimer's Consortium.

195. Sodhi AA, Younglove B, Uppalapati CK, Harrison, AM, Hull EE, Leyva KJ. **CATHEPSIN ACTIVITY AND DETECTION OF MRNA VARIANTS IN NEURAL CELLS**. Midwestern University; Arizona Alzheimer's Consortium.

196. Steele M, Wu T, Pan R. **APPLICATION OF GRAPHS TO IDENTIFY BIOMARKERS USING HUBS AND FUNCTIONAL CONNECTIVITY TO ASSESS DISEASE PROGRESSION IN ALZHEIMER'S DISEASE WITH FMRI AND PET**. Arizona State University; Arizona Alzheimer's Consortium.

197. Stewart A, Begay K, Biswas D, Yeoh-Baxter W, Serrano G, Lorenzini I, McHattie R, Doyle K. **RESOLVING ENDOGENOUS AUTOFLUORESCENCE TO ENABLE MULTIMODAL SPATIAL PROFILING OF POST-STROKE NEUROINFLAMMATION IN AGED HUMAN BRAIN.** University of Arizona, Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

198. Su CW, Sohankar J, Luo J, Li S, Su Y, Wu T, Chen K. **ACCELERATED AGING IN THE ALZHEIMER'S DISEASE (AD) BRAIN: APPLICATION OF NEURAL NETWORK MODELS TO STRUCTURAL MRI DATA QUANTIFIED USING FREESURFER 8**. Arizona State University; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

199. Sun P, Rhine K. **NEURONAL AGING AND STAU1-ASSOCIATED RNA TRANSPORT**. University of Arizona; Arizona Alzheimer's Consortium.

200. Sutherland S, Millmond E, Ekstrom A, Hill P. **SPATIAL MEMORY PRECISION AND NEUROPSYCHOLOGICAL PERFORMANCE IN OLDER ADULTS**. University of Arizona; Arizona Alzheimer's Consortium.

201. Tallino S, Newbern J, Velazquez R. **ELEVATED ITSN1 AS A LINK BETWEEN ENDOSOMAL DISRUPTION AND NEURODEGENERATION IN DOWN SYNDROME AND ALZHEIMER'S DISEASE**. Arizona State University; Arizona Alzheimer's Consortium.

202. Teluguntla K, Ugonna C, Wiskoski H, Matijevic S, Ryan L, Chen N, Trouard T. **AGE RELATED CHANGES IN COGNITIVE FUNCTION AND STRUCTURAL BRAIN CONNECTIVITY STUDIED VIA DIFFUSION MRI**. University of Arizona; Arizona Alzheimer's Consortium.

203. Trinate R, Galinsky V, Frank L, Hutchinson E. **MONTE CARLO VALIDATION OF DITSI: A NOVEL FRAMEWORK FOR CHARACTERIZING BRAIN MICROSTRUCTURE VIA**

DOUBLE DIFFUSION ENCODING MRI. University of Arizona; University of California San Diego; Arizona Alzheimer's Consortium.

204. Valentine AD, Quezada G, Zayas Abril A, Bagga I, Bakkar N, Bowser R, Medina DX. **MATRIN 3 MODULATION OF M6A LEVELS AS A NOVEL MECHANISM OF NEURODEGENERATION**. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.

205. Velez M, Harker S, Ofori E, Lewis C, Peterson D, Belnavis A, Rush M, Davila E, Phan E, Ingram L, Gallegos S, Venkatesh H, Smith-Plata J, Strasia S, Black J, Braden BB. **UNRAVELING THE LINK BETWEEN AUTISM AND PARKINSONISM: INTEGRATING CLINICAL PHENOTYPES WITH CUMULATIVE GENOMICS**. Arizona State University; Arizona Alzheimer's Consortium.

206. Wang V, Dumitrascu O. **FROM ONE READER TO MANY: A MULTI-AGENT VISION-LANGUAGE FRAMEWORK FOR RETINAL IMAGING SCREENING OF ALZHEIMER'S-ASSOCIATED ABNORMALITY**. Brophy College Preparatory; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

207. Watkins K, Leinenweber K, Yang W, DeCasien AR, O'Neill MB, Bohlen MO, Melin AD, Higham JP, Montague MJ, Platt ML, Chiou KL, Shendure J, Snyder-Mackler N. **SINGLE-NUCLEUS PROFILING REVEALS AGE-ASSOCIATED TRANSPOSABLE ELEMENT EXPRESSION ACROSS THE RHESUS MACAQUE BRAIN**. Arizona State University; University of Washington; National Institute on Aging; University of Alabama at Birmingham; University of Pennsylvania; Howard Hughes Medical Institute; Seattle Hub For Synthetic Biology; Duke University; Allen Discovery Center For Cell Lineage Tracing; New York University; New York Consortium in Evolutionary Primatology; University of Oxford; University of Calgary; Arizona Alzheimer's Consortium.

208. Waughman X, Wiskoski H, Zahra S, French SR, Arias JC, Trouard TP, Alexander GE, Weinkauf CC. **RESTING-STATE FUNCTIONAL MAGNETIC RESONANCE IMAGING REVEALS DEFICITS IN MIDDLE CEREBRAL ARTERY (MCA) INTERHEMISPHERIC CONNECTIVITY IN EXTRACRANIAL CAROTID ARTERY DISEASE**. University of Arizona College of Medicine - Tucson; Arizona Alzheimer's Consortium.

209. Wiskoski HE, Zahra S, French SR, Arias JC, Alexander GE, Weinkauf CE. **CORTICAL SURFACE AREA IS ASSOCIATED WITH MCI AND AD INDEPENDENT OF CORTICAL THICKNESS.** University of Arizona; Arizona Alzheimer's Consortium.

210. Xiong Y, Dong X, Zhu W, Li X, Dumitrascu O, Wang Y. **SGW-GAN: SLICED GROMOV-WASSERSTEIN GUIDED GANS FOR RETINAL FUNDUS IMAGE ENHANCEMENT WITH PRESERVED DISEASE-RELEVANT GEOMETRY**. Arizona State University; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

211. Yerramilli A, Hashim A, Mufson EJ, Perez SE, Verpeut JL. **CEREBELLAR SYNAPTIC DYSFUNCTION AND STRUCTURAL PLASTICITY IN ALZHEIMER'S DISEASE**. Arizona State University; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

212. Zhang H, Chou Y-h. **SEMANTIC TRAJECTORY METRICS FROM VERBAL FLUENCY: A POTENTIAL APPROACH TO CHARACTERIZING SEMANTIC SEARCH IN COGNITIVE IMPAIRMENT**. University of Arizona; Arizona Alzheimer's Consortium.

213. Zhang J, Mulder H, High N, Bauer R, Knox J, Chen Y, Nisson L, Langbaum JB, Ayers A, Huentelman M, Coon D, Pruzin J. **PODCARING: INVESTIGATING THE FEASIBILITY AND EFFICACY OF THE DEMENTIA UNTANGLED PODCAST FOR CAREGIVERS AND PERSONS WITH EARLY-STAGE COGNITIVE IMPAIRMENT**. University of Arizona College of Medicine - Phoenix; Banner Alzheimer's Institute; Banner Alzheimer's Institute - Tucson; Translational Genomics Research Institute; Arizona State University Edson College of Nursing and Health Innovation; Arizona Alzheimer's Consortium.



Arizona Alzheimer's Consortium
27th Annual Scientific Conference

Oral Research Presentation

Abstracts

ORAL RESEARCH PRESENTATION

FROM DEPRESSION SYMPTOM MANAGEMENT TO DEMENTIA PREVENTION: CONSIDERING NEXT DECADE RESEARCH, TREATMENT, AND ADVOCACY PRIORITIES TO REDUCE THE IMPACT OF DEPRESSION IN NEUROCOGNITIVE DISORDERS. Karp JF on Behalf of The International Psychogeriatric Association "Depression In NCD International Workgroup". University of Arizona College of Medicine - Tucson; Arizona Alzheimer's Consortium.

Background: Depression and mood dysregulation are among the most prevalent and clinically consequential neuropsychiatric symptoms (NCD-NPS) across the spectrum of neurocognitive disorders (NCD). These symptoms impair quality of life, increase carer burden, and are associated with accelerated functional and cognitive decline. At the same time, major depressive disorder across the lifespan represents a potentially modifiable risk factor for later-life dementia, while late-onset depressive symptoms may signal prodromal neurodegeneration. This dual role positions depression at a critical intersection between symptom management and dementia prevention.

Methods: The International Psychogeriatric Association (IPA) convened the development of a white paper and call to action that was developed through expert consensus meetings held in Buenos Aires (2024) and Kanazawa (2025). The goals were to identify key knowledge gaps and define global priorities in four domains: nomenclature, biomarkers, treatment, and prevention. These areas were selected to because current diagnostic frameworks inadequately capture dementia-specific depressive phenotypes, limiting research comparability and clinical precision. Although advances in neuroimaging, inflammatory markers, and molecular biomarkers offer promise, none are validated for routine diagnostic stratification or treatment selection. In addition, pharmacologic therapies demonstrate modest and inconsistent efficacy, and no agent is specifically approved for depression comorbid with dementia. Psychosocial and multimodal interventions remain essential but require greater scalability and integration into care systems.

Results: This presentation will describe the outcome of the IPA Depression Workgroup and share the next-decade roadmap emphasizing NCD-specific diagnostic criteria, biomarker-informed subtyping, development of targeted and scalable interventions, and integration of depression prevention into NCD care frameworks to advance precision psychiatry in NCD. Dr. Karp will also briefly address the outcomes of the other three NCD-NPS work groups – apathy, agitation, and psychosis.

Conclusions: Dr. Karp will integrate the calls to action of these workgroups into a coherent message that blends precision psychiatry, advocacy, and international priorities for education about neuropsychiatric symptoms in dementia.

ORAL RESEARCH PRESENTATION

CHARACTERIZATION OF CRYPTIC HDGFL2 PROTEIN EXPRESSION IN AMYOTROPHIC LATERAL SCLEROSIS COMPARED TO HEALTHY CONTROLS. Shahub S, Singh A, Denkinger MN, Dieckhoff K, Liu J, Marques TM, Ghisays KL, Ashton NJ. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: TDP-43 dysregulation is a defining pathological hallmark of both Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD), characterized by nuclear depletion and pathological cytoplasmic aggregation of TDP-43. Loss of normal nuclear TDP-43 function results in aberrant RNA splicing, leading to the inclusion and subsequent translation of cryptic exons in multiple transcripts, including cryptic hepatoma-derived growth factor-like protein 2 (HDGFL2-CE). Because expression of HDGFL2-CE is directly driven by TDP-43 loss-of-function pathology, it has emerged as a promising mechanistic biomarker of TDP-43 dysfunction that can be detected in biofluids such as cerebrospinal fluid (CSF) and plasma. The objective of this study was to develop a sensitive immunoassay for the quantification of HDGFL2-CE in CSF and evaluate its ability to differentiate individuals with ALS from healthy control participants.

Methods: CSF from 10 individuals diagnosed with ALS were measured for HDGFL2-CE against 10 healthy controls matched for age and gender (median age=63 years, 40% female). The immunoassay for quantification of HDGFL2-CE was developed using the Alamar NULISA qPCR custom assay development kit. HDGFL2-CE rabbit monoclonal antibodies were obtained from Yurogen Biosystems LLC (Worchester, MA, USA).

Results: The NULISA qPCR assay was optimized for quantification of HDGFL2-CE in CSF in the range of 0.05-50 pg/mL. Optimal loading volume for the assay was determined to be 50ul, at which signal obtained from pooled samples of control and ALS patients were significantly elevated over blank signal ($P<0.05$). Signal to noise ratio (SNR) of CSF obtained from healthy controls ranged from 1.13-2.57 and SNR of CSF from ALS ranged from 1.47-3.84. HDGFL2-CE was significantly elevated ($P<0.05$) in CSF of ALS patients (median=0.46; SD=0.27) over healthy controls (median=0.27; SD=0.17).

Conclusions: An ultrasensitive immunoassay for quantification of HDGFL2-CE in CSF was developed and validated against CSF samples from ALS and healthy controls. These results demonstrate the ability of HDGFL2-CE to reflect TDP-43 dysregulation in ALS compared to healthy individuals, showing promise as a stable biomarker for TDP-43 pathology in neurodegenerative disease.

ORAL RESEARCH PRESENTATION

AMBIENT AIR CONCENTRATIONS OF TOXICANTS AND RISK OF FRONTOTEMPORAL DEMENTIA. Schumacher BT, Chirag SS, Killion JA, Beyene KM, Turner J, Racette BA. Barrow Neurological Institute; Washington University; University of The Witwatersrand; Arizona Alzheimer's Consortium.

Background: Frontotemporal dementia (FTD) is a neurodegenerative disease characterized by progressive behavioral, language, and executive dysfunction. While approximately 1/3 of cases have a genetic etiology, environmental exposures likely play a role in pathophysiology. Environmental exposures, including ambient air concentrations of neurotoxicants, likely promote key mechanisms implicated in FTD neurodegeneration.

Methods: This study utilized population-based United States Medicare data to identify incident FTD cases from 2016-2018. We calculated standardized incidence ratios (SIRs) by county. Exposure measurement was derived from census-tract level ambient concentrations of 175 toxicants from the Environmental Protection Agency's 2014 National Air Toxics Assessment (NATA), a nationwide inventory of toxic air emissions, and were spatially joined to the beneficiaries' ZIP+4. We applied spatial and statistical methods to explore each toxicant individually and employed generalized weighted quantile sum (gWQS) regression to evaluate the joint association of the correlated toxicants with the risk of FTD. We used logistic regression to calculate adjusted odds ratios (aOR) and corresponding confidence intervals (CI) for each toxicant and mixtures of toxicants, adjusting for age, sex, and race.

Results: This study included 47,625 incident cases of FTD and 188,193 controls. County-level SIRs ranged from 0.4 – 115.0 (p<0.05). Our three strongest individual associations were 2,2,4-trimethylpentane (aOR: 1.09, 95% CI: 1.08-1.10), toluene (aOR: 1.08, 95% CI: 1.07-1.09), and ethylbenzene (aOR: 1.08, 95% CI: 1.07-1.09). By census tract, each one-tertile increase in the gWQS mixture was associated with 42% higher risk of FTD, adjusting for age, sex, and race (aOR: 1.42, 95% CI: 1.25 - 2.07). Geographically weighted regression elucidated unique patterns for select toxicant and U.S. regions.

Conclusions: Exposure to ambient air concentrations of select toxicants may increase risk of FTD.

ORAL RESEARCH PRESENTATION

DESIGNING AN AI CHATBOT FOR OLDER ADULTS WITH COGNITIVE DECLINE LIVING ALONE: A QUALITATIVE STUDY OF USER NEEDS AND DESIGN PRIORITIES. Gómez-Morales A, Bahrami R, Turaga P. Arizona State University; Arizona Alzheimer's Consortium.

Background: Artificial intelligence (AI)-based chatbots have the potential to support older adults experiencing age-related cognitive changes by providing personalized assistance with daily activities, health management, and social engagement. However, the successful development of AI technologies requires an understanding of end-user needs, preferences, and priorities. This study explored older adults' perspectives regarding the desired functions and design characteristics of an AI chatbot for aging in place, cognitive health, and everyday functioning.

Methods: To date, three focus groups were conducted with community-dwelling older adults (N=13). Conversations explored participants' experiences with ADRD/MCI-related cognitive changes and their perceptions of how an AI chatbot could support daily functioning, cognitive health, safety, and well-being. Focus groups held via Zoom were audio-recorded, transcribed verbatim, and analyzed using thematic analysis. NVivo and Excel were used to support data organization, coding, theme development, and figure creation.

Results: Four overarching themes were identified and translated into nine user-centered design priorities for AI chatbot development: "supporting everyday independence and organization," "promoting cognitive health and decision support," "enhancing safety while preserving independence," and "fostering social connection through accessible and personalized interaction." Participants emphasized medication management, routine reminders, cognitive stimulation activities, evidence-based health information, safety monitoring, companionship, voice-based communication, and personalized support. These findings informed nine preliminary design priorities: safety and risk mitigation; medication management; routine scaffolding; adaptive accessibility; navigation and mobility support; task sequencing and executive planning; instrumental activities of daily living; social companionship; and cognitive maintenance.

Conclusions: Older adults envisioned an AI chatbot that extends beyond information delivery to provide integrated support for daily living, cognitive health, safety, and social engagement. Findings highlight the importance of user-centered design to ensure the product developed aligns with users' needs and goals, an approach that prioritizes accessibility, personalization, and trustworthiness when developing AI technologies intended to support vulnerable aging populations. These findings provide foundational guidance for the development of user-centered AI chatbot interventions designed to support aging in place, maintain independence, and enhance quality of life among older adults experiencing cognitive changes.

ORAL RESEARCH PRESENTATION

EVALUATING POLYGENIC RISK SCORES TO PREDICT ALZHEIMER'S AND AMYLOID POSITIVITY IN AN ELECTRONIC HEALTH RECORD. Robb WH, Kaur GK, Conyers CT, Bouchal SM, Greig EE, Upjohn DP, Grilli CB, Ortega VE, Hohman TJ, Vemuri P, Ramanan VK, Koran MEI. Mayo Clinic Arizona; Mayo Clinic Florida; Vanderbilt University School of Medicine; Mayo Clinic Rochester; Arizona Alzheimer's Consortium.

Background: The emergence of anti-amyloid therapies has created an urgent need for scalable strategies to identify patients most likely to develop Alzheimer's disease (AD) and amyloid-β positivity before symptom onset. While polygenic risk scores (PRS) offer promise for precision medicine and trial enrichment, their predictive performance across real-world EHR populations, varying phenotype definitions, and distinct APOE genotype backgrounds remains incompletely characterized.

Methods: We evaluated 55 AD PRS from the PGS Catalog in 109,933 individuals aged ≥50 years across two EHR-linked cohorts (Mayo Clinic Biobank, Tapestry). PRS performance was assessed across a gradient of clinical and biomarker-confirmed phenotypes, ranging from broad ICD-derived diagnoses to confirmed amyloid positivity (Aβ+). We separated APOE from the non-APOE polygenic background and tested main and interaction effects of PRS with APOE ε4 and ε2 dosage.

Results: In fixed-effects meta-analyses, the PRS derived from the "2026 Consensus meta-analysis" consortia GWAS demonstrated the highest discriminative performance (Aβ+ vs. ICD-controls: AUC=0.80, OR=1.55 [1.40-1.71]). PRS effect sizes and predictive accuracy increased monotonically with greater phenotype specificity, from ICD-defined dementia to ICD-defined AD to Aβ+ status. In time-to-event models, both APOE and polygenic risk independently contributed to AD risk, with hazard ratios (HR) of 3.25 (95% CI: 2.98–3.54) per APOE ε4 allele and 1.43 (1.36–1.51) per SD increase in PRS, while ε2 conferred protection (HR=0.66, 0.55–0.79). Evidence for ε4×PRS interaction was weak, whereas ε2 dose attenuated PRS associations, most notably for Aβ+ outcomes (interaction HR=0.58, 95% CI: 0.39–0.85, FDR p=0.030).

Conclusions: The best-performing AD PRS in this EHR-linked population was derived from the most recent large-scale GWAS, and PRS performance improved as phenotype definitions became more biologically specific. Non-APOE polygenic risk added meaningful information beyond APOE genotype, supporting its use for genetic enrichment in amyloid screening and AD prevention trials. Furthermore, the observation that the APOE ε2 allele attenuates polygenic risk highlights a potential resilience mechanism that warrants further investigation.

ORAL RESEARCH PRESENTATION

GUT MICROBIOME DYSBIOSIS AND PARP1 ACTIVATION ARE ASSOCIATED WITH INFLAMMATORY RESPONSES IN THE BRAIN AND GUT IN ALZHEIMER'S DISEASE. Shaik S, Sheikh I, Kiela M, Doherty A, Pires P, Kiela P. Children's Research Center; University of Arizona; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder marked by synaptic loss, cognitive decline, and neuronal death. Neuropathologically, AD is defined by the accumulation of Aβ plaques and tau tangles. Although these hallmark features remain central to disease diagnosis, increasing evidence indicates that persistent neuroinflammation is a major contributor to disease progression. Chronic activation of microglia and astrocytes, together with infiltration of peripheral immune mediators, promotes the release of inflammatory cytokines, chemokines, and reactive oxygen species that can exacerbate neuronal damage. Increasing evidence implicates the brain-microbiota-gut (BMG) axis in AD progression; however, the mechanisms linking gut microbial dysbiosis to neuronal injury remain unclear. Poly (ADP-ribose) polymerase-1 (PARP1), a key mediator of inflammatory signaling and the programmed cell death 'Parthanatos', may represent a crucial mechanistic link between microbial alterations and neurodegeneration.

Methods: Male and female wild-type (WT) and 3xTg-AD mice were examined across disease progression. Brain/colonic tissues were analyzed for PARP1 activity through immunofluorescent detection of poly (ADP-ribose) (PAR) and apoptosis-inducing factor (AIF) expression. Age-dependent gut microbiome changes were characterized using 16S rRNA gene sequencing of fecal samples collected from WT (n=14) and 3xTg mice (n=18) between 1.6 and 16 months of age. Microbial diversity and differential taxonomic abundance were evaluated using standard bioinformatic and statistical approaches. To assess functional relevance, germ-free mice (GF) were colonized with microbiota from aged WT or 3xTg donor mice (16 months).

Results: PARylation was significantly increased in brain and colon of 3xTg mice compared with WT controls and progressively increased with age. Female 3xTg mice exhibited the highest PAR accumulation, indicating sex-dependent enhancement of PARP1 activity. Increased PARP1 and AIF expression in the colonic epithelium further supported activation of PARP1. Microbiome analysis identified 1,263 ASVs and revealed significant genotype-by-age interactions in alpha diversity, demonstrating impaired age-related microbial diversification in 3xTg mice. Community composition progressively diverged with aging, driven primarily by shifts in low-abundance taxa. Differential abundance testing identified 27 altered genera, including depletion of short-chain fatty acid-producing and bile acid-metabolizing taxa and enrichment of Erysipelotrichaceae and other inflammation-associated bacterial groups. Donor inocula from aged WT and 3xTg mice faithfully recapitulated genotype-specific microbial signatures, including depletion of Bacteroidota-associated taxa and expansion of Lactobacillaceae and Erysipelotrichaceae in 3xTg donors. These findings validate the donor pools for ongoing FMT studies investigating the contribution of AD-associated microbiota to neuroinflammatory signaling and brain transcriptional responses.

Conclusions: Our findings demonstrate that AD-associated gut microbial dysbiosis occurs in parallel with increased PARP1 activation along the gut-brain axis. Age-dependent loss of beneficial microbial taxa and enrichment of pro-inflammatory bacterial communities coincide with elevated PARylation in both central and peripheral tissues, particularly in females. Together, these data support a model in which microbiome alterations promote chronic inflammatory signaling and PARP1 activation. Ongoing FMT studies will determine whether AD-associated microbial communities directly drive PARP1-dependent neuroinflammatory responses. Our work identifies microbiome–PARP1 interactions as a potential therapeutic target for modifying AD progression.

ORAL RESEARCH PRESENTATION

ULTRASENSITIVE IMMUNOASSAY FOR PLASMA EMTBR-243 FOR TRACKING TAU TANGLE PATHOLOGY IN ALZHEIMER'S DISEASE. Singh A, Denkinger MN, Serrano GE, Beach TG, Reiman EM, Janelidze S, Hansson O, Rosa-Neto P, Mattsson-Calgren N, Ashton NJ. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Lund University; UT Southwestern Medical Center; McGill University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) pathology is marked by amyloid (Aβ) deposits and tau tangles, which can be confirmed either via post-mortem examination or using positron emission tomography (PET), cerebrospinal fluid (CSF), and, more recently, blood biomarkers. Phosphorylated tau esp., pTau217 is currently the leading blood biomarker for AD for tracking amyloid-β pathology and early tau changes. However, there are no biomarkers for tracking tau tangle pathology that strongly correlates with cognitive decline. Recent studies have identified eMTBR-243, a tau fragment encompassing amino acids 243–254 within the microtubule-binding region, as a promising biomarker of tau tangle pathology. In this study, we demonstrate a novel Nucleic Acid-Linked Immuno-Sandwich Assay (NULISA™) singleplex immunoassay for the quantification of eMTBR-243 in plasma.

Methods: We examined a total of 477 participants (217 [45.5 %] female; mean [SD] age, 79.7 [7.7] years). Firstly, we measured eMTBR-243 in 280 participants from Brain & Body Donation Program (BBDP) at Banner Sun health research institute (Neuropathology Cohort), with matched antemortem blood samples and post-mortem neuropathological assessment. Secondly, we evaluated Spearman correlation between plasma eMTBR-243 levels and tau PET measures in two observational research cohorts with tau: The Translational Biomarkers in Aging and Dementia (TRIAD) cohort (N = 88) with MK6240 (PET Cohort I) and the Swedish BioFINDER Cohort (N = 109) with RO-6958948 (PET Cohort II).

Results: In the neuropathology cohort, NULISATM eMTBR-243 levels significantly increased from Braak IV (median (pg/ml) 0.005, IQR 0.003 - 0.008), Braak V (0.023, 0.01- 0.05) and Braak VI (0.078, 0.045 - 0.18 compared to earlier Braak stages ($p < 0.001$). Similarly, in PET Cohort I, NULISATM eMTBR-243 levels were significantly higher in Braak IV (0.029, 0.017 - 0.032), Braak V (0.043, 0.034- 0.062), Braak VI (0.074, 0.063 - 0.136) as compared to earlier Braak stages. In PET Cohort II, we examined the correlations between eMTBR-243 and Tau PET SUVR. The strength of the association was significant in all Braak regions; Braak I-II ($r = 0.85$, $p < 0.001$), III-IV ($r = 0.84$, $p < 0.001$), and V-VI ($r = 0.81$, $p < 0.001$). In the amyloid positive group only, the association of eMTBR-243 and tau PET increased in later Braak regions (Braak I-II, $r = 0.39$; $p = 0.006$; III-IV, $r = 0.69$, $p < 0.001$; V-VI, $r = 0.82$, $p < 0.001$). In PET Cohort II, we observed high accuracy (AUC [95% CI]: 0.962 [0.924-1.00], 0.987 [0.973-1.00], 0.987 [0.97-1.00]) for discriminating tau-positivity in Braak I-II, III-IV, and V-VI regions, respectively.

Conclusions: In this study, we report a novel immunoassay for the accurate quantification of plasma eMTBR-243 that demonstrates strong concordance neuropathologically confirmed Braak stages. When combined with Core 1 biomarkers of amyloid pathology such as pTau217, this supports the potential role of plasma eMTBR-243 as a complementary Core 2 biomarker for assessing tau tangle burden, disease stage, and severity.

ORAL RESEARCH PRESENTATION

AUTISM GENETIC LIABILITY IN ALZHEIMER'S DISEASE AND RELATED NEUROPATHOLOGY. Harker SA, Serrano G, Aslam S, Piras IS, Shablin AS, Huentelman MJ, Taguinod F, Braden BB, Lewis CR. Arizona State University; Banner Sun Health Research Institute; Translational Genomics Research Institute; University of Utah; Arizona Alzheimer's Consortium.

Background: Multiple independent healthcare record sources have demonstrated that adults with autism spectrum disorder (ASD) are at increased risk for Alzheimer's disease (AD) and related dementias. The biological mechanisms driving the convergence between neurodevelopmental and neurodegenerative conditions are largely unknown. Autism has a strong genetic basis with heritability estimates ranging from 50-80%; therefore, autism genetic liability may confer risk for AD and related neuropathology.

Methods: Neuropathology-confirmed AD diagnoses included 466 cases and controls included 258 without mild cognitive impairment/dementia during life and a major neuropathological diagnosis. No participants had known ASD diagnoses. Autism polygenic risk scores (PGS) were generated, and participants were binned into ASD-PGS quartiles with Q1 as the bottom 25% of least risk and Q4 as the top 25% greatest risk. The Consortium to Establish a Registry for Alzheimer's Disease templates were used to score tangles and plaques as none, sparse, moderate, and frequent, converted to 0-3 for analysis.

Results: PGS quartiles were used to model non-linear relationships and aid in interpretation. All models adjusted for postmortem interval, age at death, gender, the AD-PGS, and the first 9 principal ancestry components. Autism-PGS was associated with AD status with individuals in the highest risk quartile (Q4) exhibiting the highest odds of AD compared to Q1-3 ($p<0.05$). In controls, Autism-PGS was associated with greater plaque burden across multiple regions and entorhinal tangle burden (all p's<0.05 false discovery rate [FDR] corrected), but there were no Autism-PGS associations in AD cases, consistent with a ceiling effect of pathology.

Conclusions: Findings indicate that autism genetic liability may reflect shared biological pathways influencing AD neuropathology. Importantly, with the relatively recent (1980) inclusion of autism in the DSM, adults with confirmed autism diagnoses have historically not been included in AD neuropathology research. Therefore, many of the participants in the highest quartile of ASD genetic liability could be undiagnosed autistic adults. These are some of the first biological insights on the convergence of ASD and AD diagnosis, which suggest potentially greater canonical AD neuropathology associated with autism, as opposed to autism-specific brain aging mechanisms alone. Future neuropathology research in those with confirmed autism diagnoses is warranted. Elevated autism polygenic risk may contribute to variability in AD risk and neuropathology.

ORAL RESEARCH PRESENTATION

IMPACT OF LIVER DYSFUNCTION AND TRANSPLANTATION ON CNS AND INFLAMMATORY BLOOD BIOMARKERS. Greig EE, Robb WH, Denkinger MN, Bouchal SM, Singh A, Hohman TJ, Dickson R, Jaramillo A, Ashton NJ, Koran MEI. Mayo Clinic Florida; Mayo Clinic Arizona; Banner Sun Health Research Institute; Vanderbilt University Medical Center; The Sahlgrenska Academy at The University of Gothenburg; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Blood proteomics are increasingly being used in neurodegenerative disease evaluation and diagnosis including Alzheimer's disease (AD), but understanding the influence of systemic organ function remains critical. Emerging evidence indicates that concentrations of peripheral biomarkers, including tau, are influenced by systemic organ dysfunction, confounding diagnosis and limiting widespread clinical utility. In this study, we evaluated 131 circulating proteins including total and brain-derived (BD) phosphorylated tau species in patients ~4 weeks before and 4-12 months after liver transplant (LT), assessing the stability of these blood-based biomarkers within the same patient across the extremes of liver function.

Methods: 55 patients over the age of 65 received an LT at Mayo Clinic Arizona. Serum concentrations of Central Nervous System (CNS) and immune proteins were assessed via the NULISAseq 120-plex CNS Disease Panel. Linear mixed-effects models assessed change within patients pre- and post- transplant and in protein concentrations relative to changes in liver function via the Model for End-Stage Liver Disease (MELD) 3.0 score.

Results: At either post-LT time point, 109/131 (84%) of CNS disease panel proteins significantly changed. 72 proteins were significantly different at both 4- and 12-months post-LT and changed in consistent directions. The greatest proportion of proteins classified as DNA and/or RNA defects, Altered Energy Homeostasis, and Pathological Protein Aggregation changed post-LT (using Alamar classification). All total tau measures decreased after LT, as did BD-pTau181 and pTau231 at 4-months (β=-0.374, p=0.008; β=-0.887, p<0.001 respectively). Results were similar at 12-months. Almost 1/3 of patients would have been incorrectly labeled pTau217+ pre-LT and became negative post-LT. Both BD-MAPT and BD-pTau217 did not significantly change after LT (p>0.05). Greater changes in MELD were associated with greater change in biomarkers.

Conclusions: This study suggests that circulating plasma proteins associated with CNS processes and immune response are altered due to liver dysfunction, including the clinically implemented pTau217, perhaps due to alterations to hepatic clearance, production, or inflammatory pathways. Of note, BD-MAPT and BD-pTau217 did not change post-LT, suggesting that these biomarkers may be more reliable in populations with liver dysfunction. Future studies are needed to validate these findings in a larger cohort and compare elevations in protein concentrations to ground truth.

ORAL RESEARCH PRESENTATION

HEARING AGE: A SCALABLE ONLINE MEASURE OF HIGH-FREQUENCY HEARING HEALTH FOR AGING RESEARCH WITHIN THE MINDCROWD PLATFORM. Manna K, Venkatachalam H, Johnson M, Sharma S, De Both M, Alford K, Mendoza D, Schrauwen I, Huentelman M. University of Arizona College of Medicine – Phoenix; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Hearing loss is strongly associated with cognitive decline and increased risk for Alzheimer's disease (AD), but most hearing-cognition research depends on clinical audiometry and limiting scalability. Additionally, at larger scale, hearing is often investigated via self-reports or medical codes, overlooking the progressive nature of hearing that occurs with aging. The human hearing frequency range spans approximately 20 Hz to 20,000 Hz, though the upper limit of perceivable frequencies naturally decreases with age, making high-frequency hearing tests a useful measurement of overall hearing health. Here, we developed a new online test within the MindCrowd platform that estimates an individual's highest detectable frequency and offers a measure of hearing health relative to chronological age. We validate this test in the MindCrowd cohort on an initial group of 1049 participants and examine its association with population demographics. The test was designated as "Hearing Age".

Methods: Participants who completed the MindCrowd Hearing Age test, PAL memory test, and simple visual reaction time (svRT) test were included (N = 852, ages 19–88). The Hearing Age test employs three rounds of a linear frequency sweep (125 Hz–21 kHz over 60 seconds) preceded by a 500 Hz calibration step; participants indicate when they can no longer hear the ascending tone, yielding a highest detectable frequency for each round. Quality control removed invalid responses (20,100 Hz) and excluded rounds with high within-session variability (SD across rounds > 10 seconds). Linear regression tested predictors of hearing frequency (age, sex, and their interaction) with Type II ANOVA. All data analyses were conducted in R.

Results: After quality control, 92% of sessions (962/1049) were retained. Hearing frequency declined significantly with age ($\beta = -153$ Hz/year, $p < 2.2 \times 10^{-16}$), with age explaining ~50% of variance, validating the test's ability to capture expected audiometric patterns remotely. Males aged 60+ showed significantly worse hearing than females (−570 Hz, $p = 0.005$), with males declining ~47 Hz/year faster from midlife onward (age × sex interaction, $p = 0.009$ in 40+ subset). Self-reported hearing loss (−1,477 Hz, $p < 2.2 \times 10^{-16}$), tinnitus (−349 Hz, $p = 0.031$), and headphone type ($p = 9.3 \times 10^{-10}$) were significant predictors after adjusting for age and sex.

Conclusions: The MindCrowd Hearing Age test is a scalable online instrument that reliably captures age-related auditory decline and replicates established sex-differential hearing patterns in a community-based cohort. Additional work to be presented at the meeting will include: 1) comparing this test to a well-established online hearing test (speech-in-noise test) also integrated within the MindCrowd platform; 2) development of a predictive model of age ("hearing age") based on the current cohort; 3) investigation of the two hearing tests and differences between chronological age and predicted age based on hearing in relation to other assessments and self-reported measures within the MindCrowd platform, including memory performance and Alzheimer's disease risk. By embedding hearing assessment with the MindCrowd platform alongside memory and attention tests, this work establishes a foundation for longitudinal investigation of the hearing-dementia link at population scale.

ORAL RESEARCH PRESENTATION

REPURPOSING THE FDA-APPROVED A-GLUCOSIDASE INHIBITOR MIGLITOL FOR ALZHEIMER'S DISEASE: EFFECTS IN APOE3/E4 BRAIN ORGANOIDS AND 3XTG-AD MICE.
Gendron W, Feng L, Winslow W, Umaiyalan VR, Gaikwad R, Chan Y, Wang Q, Lim ET, Velazquez Jr. R. Arizona State University; University of Massachusetts Chan Medical School; Arizona Alzheimer's Consortium.

Background: Efforts to repurpose FDA-approved therapies have emerged as a strategy to find alternative disease-modifying treatments for AD. We recently identified the diabetics drug target α-glucosidase MGAM as a novel drug repurposing target for AD. Miglitol (MIG), an MGAM inhibitor, may provide neuroprotective benefits by restoring systemic metabolic balance. Individuals carrying the APOE4 allele are at a higher risk for developing AD and are vulnerable to metabolic and inflammatory stressors. Targeting peripheral physiology is a promising therapeutic strategy because systemic metabolic dysfunction often precedes and accelerates AD pathology. We therefore investigated whether MIG reduces AD-related neuropathological and inflammatory markers in APOE33 (E33) vs E44 (E44) human AD brain organoids and in 3xTg-AD mice.

Methods: We differentiated 7-month-old 2D dissociated cells from cerebral organoids (dcOrgs) using induced pluripotent stem cells from E33 or E44 donors. 200uM of MIG treatment was introduced to mock dcOrgs or herpes simplex virus 1 (HSV-1) infected dcOrgs that model neuroinflammation associated with AD in-vitro. These samples were RNA sequenced. In parallel, at 7.5 months of age, 3xTg-AD mice received oral administration of vehicle, 10 or 30 mg/kg of MIG for 30 consecutive days (n = 3–4 per group; sex-balanced cohorts). We used Enzyme-linked immunosorbent assays to quantify plasma glial fibrillary acidic protein (GFAP), a marker of neuroinflammation, neurofilament light chain (NfL), a marker of neuroaxonal injury, and AD–related pathological markers, including soluble (sol) and insoluble (insol) Aβ40 and Aβ42 and phosphorylated tau (pTau Serine (S) 396, Threonine (T)231, and T217).

Results: MIG treatment on HSV-1-infected dcOrgs had significantly more differentially expressed genes (DEGs) in E33 compared to E44. Several MGAM downstream target genes were solely rescued in MIG-treated and infected E33 dcOrgs. No differences in DEGs were seen between MIG treated mock E44 and E33 dcOrgs, indicating that the effects of MIG occur only in HSV-1-infected dcOrgs. MIG treatment at 30 mg/kg was the most effective at decreasing sol and insol Aβ40 and Aβ42 in 3xTg-AD mice. In females, 30 mg/kg MIG reduced sol and insol pTau T217, as well as insol T231 and S396. At 30 mg/kg, males showed a reduction in insol S396. GFAP and NfL were significantly reduced with treatment, highlighting blood-based biomarker tracking to monitor treatment-associated changes.

Conclusions: These findings support the repurposing of MIG as a strategy for AD that may confer meaningful neuroprotective effects in the degenerating brain.

ORAL RESEARCH PRESENTATION

A NON-INFERIORITY EVALUATION OF DIGITAL DISCLOSURE: A SCALABLE ALTERNATIVE FOR RETURNING ALZHEIMER'S GENETIC AND BIOMARKER RESULTS. Erickson C, Langlois C, McCarty Wood B, Egleston B, Harkins K, Mim R, John S, Ofidis D, Enos J, Salata H, DeSantiago D, Largent E, Reiman EM, Denkinger MN, Ashton NJ, Roberts S, Karlawish J, Bradbury A, Langbaum JB. Banner Alzheimer's Institute; University of Pennsylvania; Fox Chase Cancer Center; Banner Sun Health Research Institute; University of Michigan School of Public Health; Arizona Alzheimer's Consortium.

Background: Blood biomarkers (BBM) and genetic testing are poised to transform Alzheimer's disease (AD) risk assessment, particularly with anticipated broader clinical adoption of plasma pTau-217 assays alongside *APOE* genotyping. At the same time, due to the 21st Century Cures Act, patients in the U.S. are increasingly learning AD-related test results through electronic health portals. Together, the confluence of demand for AD-related testing, shortage of genetic counselors and dementia specialists, and healthcare policy which generally requires immediate return of medical test results, heighten the need to identify alternative scalable delivery models of AD risk information that are safe, comprehensible, and also minimize healthcare system burden.

Methods: The Evaluation of Self-mediated Alternatives for Risk Testing Education and Return of results (eSMARTER) study is a randomized, non-inferiority clinical trial to evaluate self-directed digital interventions for returning *APOE* (primary) and pTau-217 results (exploratory) to adults aged 60–80 years. After consent, the baseline survey, and optional digital education, participants were randomized 2:1 to digital or clinician-mediated telehealth return of results. *APOE* return of results occurred first. Patient-reported outcomes (PROs) were collected at baseline (T0), 2-7 days (T1), 6 weeks (T2), and 6 months (T3) following *APOE* disclosure. After T3, participants had the option to learn their pTau-217 result. Plasma p-Tau217 concentrations were measured on the Roche cobas e801 platform using a Research Use Only (RUO) assay. Thresholds were developed resulting in three stratification levels: negative, intermediate, and positive. PROs were collected 2-7 days (T4), and 4 weeks (T5) after return of pTau-217 results. The three primary non-inferiority outcomes were changes in anxiety, genetic knowledge, and disease-specific distress (T0-T1). Non-inferiority was concluded if the upper bound of the 96.7% confidence interval did not cross the pre-defined non-inferiority threshold in a direction that would favor clinician-mediated return of results.

Results: Results: 674 persons (mean [SD] age 68 [4.7] years; 451 [67%] female; mean [SD] telephone MoCA=19 [2]) were eligible and provided demographic information. 651 participants were randomized to clinician-mediated (n=216) or digital disclosure (n=435) and completed APOE disclosure (66 [10%] *APOE4* homozygotes, 377 [58%] heterozygotes, 208 [32%] non-carriers). Baseline characteristics were balanced across groups. 604 participants completed the study; 500 completed optional pTau-217 disclosure. pTau-217 results were: 47% negative, 31% intermediate, and 22% positive. At 1-7 days following *APOE* disclosure, scores on AD-related knowledge, PROMIS Anxiety, and disease-specific distress measures met non-inferiority. Non-inferiority was also met for these outcomes at T0-T2 and T0-T3. For pTau-217 disclosure, comparisons between the digital and clinician-mediated arms did not reach significance on measures of BBM knowledge at T4 (p=0.58) and T5 (p=0.80), T3-T4 change in anxiety (p=0.79) or disease-specific distress (p=0.07), and T3-T5 change in anxiety (p=0.31) or disease-specific distress (p=0.74). Analyses of other secondary PROs and moderator analyses are ongoing.

Conclusions: Disclosure of *APOE* genotype by the eSMARTER digital platform is non-inferior to clinician-mediated telehealth disclosure. No significant between group differences were found following disclosure of pTau-217 results. Together, these results suggest that this digital platform may provide an evidence-based scalable approach for returning AD genetic and biomarker results.

Arizona Alzheimer's Consortium
27th Annual Scientific Conference

Poster Presentation

Abstracts

POSTER # 1

TOO HOT TO REMEMBER? A SCOPING REVIEW OF CLIMATE HEAT AND ALZHEIMER'S DISEASE AND RELATED DEMENTIAS RISK. Acevedo-Molina MC, Wang I, Killion JA, Racette BA, Karway GK. Barrow Neurological Institute; Washington University in St. Louis; Creighton School of Medicine; Arizona Alzheimer's Consortium.

Background: Climate change and extreme heat pose significant health risks to older adults, particularly individuals with Alzheimer's disease and related dementias (ADRD). However, the relationship between heat exposure and ADRD is poorly understood. Therefore, the primary objectives of this project were to identify, synthesize, and characterize the existing literature examining the relationship between extreme ambient heat exposure and ADRD.

Methods: This scoping review utilized a comprehensive search strategy encompassing PubMed, Embase, Scopus, CINAHL, Cochrane Library, PsycINFO, Springer Open Access, Google Scholar, ClinicalTrials.gov, and ProQuest. Additionally, backward and forward citation searches were performed to identify relevant literature. Inclusion criteria focused on studies investigating the relationship between heat exposure, climate change, temperature variability, or heat waves and ADRD-related outcomes, including but not limited to hospitalization, behavioral disturbances, worsening cognitive symptoms, and mortality. Data extraction captured study design, geographic setting, exposure assessment methodologies, population characteristics, and primary findings. Catchii systematic review software facilitated screening and data management. The review process was guided by the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA ScR).

Results: Out of 163 initial articles, 16 met the inclusion criteria. A subsequent snowball search yielded another 13 articles, bringing the total to 29 studies. A significant geographic imbalance was observed, with most studies originating from China and relatively few from the United States. Current evidence broadly links extreme heat exposure to increased risks of hospitalization, mortality, behavioral disturbances, and the exacerbation of cognitive symptoms in individuals with ADRD. Consistent findings highlighted the particular vulnerability of older adults with ADRD to heat-related harms, specifically due to impaired thermoregulation, reduced adaptive capacity, social isolation, and coexisting chronic conditions. Disparities in these outcomes were also reported, often tied to socioeconomic status, housing conditions, and limited access to cooling resources. Despite these insights, methodology and findings varied significantly across regions, and there is a notable scarcity of longitudinal evidence examining long-term impacts.

Conclusions: As global temperatures continue to rise, understanding the relationship between climate-related heat exposure and ADRD is increasingly important for public health and clinical care. Existing evidence identifies individuals living with ADRD as a particularly vulnerable population during extreme heat events; however, the literature remains geographically limited, with few studies conducted in the United States. Additional longitudinal and community-based research is needed to better understand underlying mechanisms, long-term cognitive impacts, and effective prevention strategies to support equitable, climate-resilient dementia care and public health interventions.

POSTER # 2

COMPARING TASSO+ TO VENOUS BLOOD-BIOMARKER LEVELS: A VALIDATION STUDY.
Atri T, Denkinger MN, Liu J, Singh A, Surdyn M, Brown V, Martinez G, Kuramoto A, Marques TM, Langbaum JB, Atri A, Ashton NJ. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Plasma phosphorylated tau-217 (p-tau217) has been shown to accurately reflect the presence of brain amyloid-beta plaques, one of the pathological hallmarks of Alzheimer's disease (AD). Conventional blood collection relies on venipuncture, which presents logistical challenges, including the need for trained and accessible phlebotomists. Consequently, there is a need for novel remote blood collection methods that can provide accurate measurements of p-tau217 and other biomarkers. In this study, we evaluated the Tasso+ capillary blood collection device as a scalable remote sampling approach for biomarker testing and assessed its ability to accurately measure neurodegeneration-related biomarkers.

Methods: Participants were recruited at Banner Sun Health Research Institute (Sun City, Arizona, USA) as part of the DROP-AD 2.0 study. A total of 83 participants (57 [69.7%] female; mean [SD] age, 78.8 [8.2] years) spanning the cognitive continuum from cognitively unimpaired to mild cognitive impairment (MCI) and dementia were included in the present analysis. Plasma p-tau217 was measured in all venipuncture samples using the cobas® e 801 platform (Roche Diagnostics) and served as the reference standard for AD biomarker status classification based on established cutoffs (Denkinger, AAIC 2025). In addition, 131 central nervous system–related proteins were quantified in Tasso+ and venous plasma using the Nucleic Acid Linked Immuno-Sandwich Assay (NULISA™) CNS panel. Statistical analyses were performed in R (version 4.5.2) using Rstudio.

Results: Consistent with previous reports, only a weak correlation was observed between venous and Tasso+ levels of p-tau217 when measured directly ($R = 0.29$, $p = 0.0079$). Direct comparison of p-tau217 measured using the NULISA™ platform demonstrated significantly higher concentrations in Tasso+ samples than in matched venous plasma samples (mean [variance] NPQ: 13.29 [0.63] Tasso vs 10.95 [0.73] venous, $p = 1.72 \times 10^{-41}$). The strongest Tasso+ ratio relationship was observed for the BD-p-tau217/BD-p-tau181 ratio, which demonstrated a robust correlation with venous Roche p-tau217 concentrations ($R = 0.76$, $p < 2.2 \times 10^{-16}$). In contrast, neurofilament light (NfL) ($R = 0.95$, $p < 2.2 \times 10^{-16}$) and glial fibrillary acidic protein (GFAP) ($R = 0.96$, $p < 2.2 \times 10^{-16}$) showed excellent agreement between venous and Tasso+ plasma without the need for normalization or ratio-based approaches. Out of all 131 biomarkers probed, 47 (35.9%) had a Pearson R greater or equal to 0.90, 29 (22.1%) were between 0.70 and 0.90, and 25 (19.1%) had values between 0.30 and 0.70. 30 (22.9%) biomarkers had values less than 0.30.

Conclusions: Although direct quantification of p-tau biomarkers showed substantial matrix-related differences between venous and capillary samples, ratio-based normalization strategies—particularly the BD-p-tau217/BD-p-tau181 ratio—substantially improved concordance and showed strong agreement with clinically validated venous p-tau217 measurements. In parallel, the excellent venous-capillary agreement observed for established neurodegeneration markers, including NfL and GFAP, demonstrates that remote blood collection can reliably support measurement of multiple central nervous system biomarkers. Collectively, these findings highlight the potential of remote sampling technologies to expand access to biomarker-based screening, enable decentralized recruitment for AD prevention trials, and support future large-scale public health screening initiatives. Importantly, biomarker-specific validation remains essential, as assay performance varied considerably across analytes. Ongoing validation in an independent replication cohort, including comparison against amyloid PET imaging, will determine the clinical utility of capillary blood-based p-tau biomarker strategies for early AD detection.

POSTER # 3

MANUAL LYMPH DRAINAGE IN A MURINE MODEL OF ALZHEIMER'S DISEASE ATTENUATES COGNITIVE IMPAIRMENT AND BIOMARKERS OF DISEASE. Bartlett MJ, Erickson RP, Polk FD, Frye F, Doyle KP, Pires PW, Witte MH. University of Arizona College of Medicine - Tucson; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) affects 6.9 million people over the age of 65 years in the US and is expected to double by 2060. While FDA approved immunotherapies slow cognitive decline in some individuals with AD, they do not improve cognition, are costly, and have significant side-effects. Therefore, new targets, approaches, and treatments for AD is an immediate necessity. Currently, there are no FDA approved therapies for AD that target the brain's lymphatic system. Recent literature has demonstrated that the toxic protein, amyloid-beta (Aβ), which accumulates in the AD brain is cleared with interstitial and cerebrospinal fluid through a glymphatic—meningeal lymphatic vessel—deep/superficial cervical lymphatic vessel pathway. Therefore, any impairment along this route can lead to inefficient drainage and pathological accumulation of Aβ, progressing to cognitive decline and eventually AD. We propose a new approach to treating AD, manual lymphatic drainage (MLD), a light skin massage technique traditionally used to reduce fluid accumulation in lymphedema. We hypothesize that MLD targeting the cervical lymphatic vessels will improve cognitive function in AD by increasing Aβ removal from the brain.

Methods: To test this hypothesis, 5-month-old 5xFAD mice were treated with MLD for 15-minutes, twice per day, for two months. This was followed by behavioral testing to determine changes in cognitive function via the Y-maze and nest building tests. After completing behavioral testing, plasma and brain tissue was collected to further investigate the impact of MLD on biomarkers of AD. First, we analyzed the effect of MLD on plasma neurofilament light chain (NfL) via a single molecule array assay. This was followed by ELISA analysis of amyloid-beta.

Results: In this preclinical model of AD, 5xFAD mice have significantly reduced nest building scores (One-way ANOVA, Kruskall-Wallis Dunns post-hoc analysis; $^{**}p<0.01$; n=6-9 mice/group) and percent spontaneous alternation in the Y-maze (One-way ANOVA, Fisher's LSD post-hoc; $^{*}p<0.05$; n=6-12 mice/group) compared to WT mice. This cognitive impairment was attenuated in both behavioral tests in 5xFAD mice treated with MLD ($^{*}p<0.05$). Following behavior, we then analyzed both NfL and amyloid-beta changes in 5xFAD mice. Sham-treated and MLD-treated 5x-FAD mice have significantly elevated plasma NfL compared to wild type (WT) mice. However, MLD significantly reduced plasma NfL compared to sham-treated 5x-FAD mice suggesting a therapeutic effect (one-way ANOVA, with a Fisher's LSD post hoc test; $^{*}p<0.05$; n=5 mice/group). We found a similar effect of MLD on the AD-specific biomarker, Aβ. The $A\beta_{42/40}$ ratio is significantly increased in the hippocampus of sham-treated and MLD-treated *5x-FAD* mice compared to WTs. Here, MLD also significantly reduced the hippocampal $A\beta_{42/40}$ ratio compared to sham-treated *5x-FAD* mice (one-way ANOVA, with a Fisher's LSD *post hoc* test; $^{*}p<0.05$; n=5 mice/group).

Conclusions: In conclusion, there is no approved therapy that directly targets the brain's lymphatic system for the treatment of AD, or any neurodegenerative disease. MLD has previously been used for the treatment of lymphedema but has also been shown to be safe to use for individuals with dementia, specifically reducing agitation and increasing social contact in this population. However, the effects of MLD on cognition and biomarkers of AD has not been investigated. Here, for the first time, we propose MLD as a potential therapy that may reduce cognitive impairment and disease-modifying biomarkers in AD. This proof-of-principle pilot data lays the foundation for further investigation of MLD as a therapy for AD. Moreover, as MLD is already approved in humans, it can be translated immediately as a stand-alone or adjunct therapy.

POSTER # 4

HPBCD-MEDIATED LIPID CLEARANCE REDUCES CHRONIC POST-STROKE INFLAMMATION AND PROMOTES IMMUNE RESOLUTION. Becktel D, Frye J, Le E, Whitman S, Doyle K. University of Arizona; Arizona Alzheimer's Consortium.

Background: Ischemic stroke causes the substantial release of lipid debris from injured brain tissue, which accumulates within infiltrating monocytes and resident microglia, promoting a "foamy" or lipid-laden phenotype. Lipid overload disrupts myeloid lipid catabolism, impairs phagocytic function, delays inflammatory resolution, and sustains neurotoxic signaling, contributing to delayed cognitive impairment. Despite its importance, the mechanisms linking lipid dysregulation to persistent immune activation after stroke remain incompletely understood. Here, we present an integrated analysis of lipid-immune interactions after ischemic stroke and evaluate 2-hydroxypropyl-β-cyclodextrin (HPβCD), a cholesterol-binding agent, as a tool to modulate post-stroke lipid accumulation and inflammatory signaling.

Methods: A distal middle cerebral artery occlusion model was used in young adult and aged mice to characterize lipid dysregulation during acute and chronic phases of ischemic injury. HPβCD was administered during acute, subacute, and chronic phases to assess its effects on lipid metabolism, immune activation, and stroke recovery. Lipidomic profiling of plasma and stroke infarcts, along with transcriptional profiling and histological analyses of infarcts and functionally affected brain regions, was performed to evaluate lipid accumulation, inflammatory signaling, immune cell infiltration, neuronal integrity, and functional recovery.

Results: Ischemic stroke induced pronounced disruptions in lipid homeostasis across both acute and chronic phases of injury. Acute plasma lipidomic profiling revealed elevations of myelin-derived sphingolipids, including sphingomyelins and hexosylceramides, reflecting rapid brain lipid catabolism. In parallel, chronic stroke infarcts accumulated sphingomyelins, sulfatides, and cholesterol esters, implicating these lipid species in sustained myeloid dysfunction. Chronic plasma signatures were further characterized by persistent elevations of pro-inflammatory arachidonic acid derivatives, including 12-hydroxyeicosatetraenoic acid (12-HETE), consistent with prolonged inflammation. These results demonstrate a temporal coupling between lipid accumulation and persistent immune activation, providing a mechanistic rationale for therapeutic targeting of lipid clearance.

To directly test this mechanistic link, we evaluated HPβCD, which demonstrated rapid systemic distribution and selective accumulation within the ischemic hemisphere during periods of blood-brain barrier disruption. Although acute administration did not provide immediate neuroprotection, HPβCD induced plasma lipidomic signatures consistent with enhanced lipid clearance, reduced pro-inflammatory oxylipin production, and increased cholesterol metabolism. Repeated administration during subacute and chronic phases reduced lipid droplet accumulation and adaptive immune cell infiltration within infarcts, downregulated immune and chemotactic transcriptional programs, preserved neuronal integrity, and improved functional recovery.

Conclusions: These results identify lipid dysregulation as a central driver of chronic post-stroke immune activation, establish plasma lipid species as biomarkers of neurodegeneration and persistent inflammation, and highlight HPβCD-mediated lipid clearance as a mechanistically informed strategy to promote immune resolution and functional recovery after ischemic stroke.

POSTER # 5

FREE-WATER ELIMINATION DIFFUSION MRI DETECTS LONGITUDINAL WHITE MATTER REMODELING IN THE 3XTG-AD MOUSE MODEL. Bergamino M, Fuentes A, White J, Winslow W, Velazquez R, Stokes A. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is associated with microstructural damage and neuroinflammation that precede overt brain atrophy. Although MRI-based diffusion tensor imaging (DTI) is sensitive to these alterations, conventional metrics such as fractional anisotropy (FA) are strongly influenced by extracellular free-water contamination. Here, we used multi-shell diffusion MRI (dMRI) with a free-water elimination framework to derive extracellular free-water fraction (fw-F) and free-water-corrected FA (fw-FA). The longitudinal evolution of these biomarkers was assessed in the 3xTg-AD mouse model and non-transgenic (NonTg) controls to characterize the progression of extracellular remodeling and neurodegeneration associated with AD pathology.

Methods: This study included 19 NonTg and 17 3xTg-AD mice (all female). Mice were imaged on a Bruker 7T scanner at 3 months (TP1), 8 months (TP2), and 13 months (TP3). At TP1 and TP2, tissue was collected from a subset of animals from each group to be used for histopathological validation, with 13 WT and 11 3xTg mice remaining at TP3. dMRI data were preprocessed using denoising, eddy-current correction, and coregistration to a standard mouse template. fw-F and fw-FA maps were analyzed using voxel-based statistics. Longitudinal effects were assessed using a linear mixed-effects model including fixed effects of Group, TimePoint, Group×TimePoint interaction, and Age. In addition, separate linear models were applied at each time point to characterize disease progression over time. Effect sizes were quantified using omega squared (ω^2) and Hedges' g, and statistical significance was corrected using probabilistic threshold-free cluster enhancement (pTFCE) and false discovery rate (FDR) correction.

Results: Voxel-wise longitudinal analysis revealed a significant main effect of group, with 3xTg-AD mice showing higher fw-F and lower fw-FA compared with NonTg animals, predominantly within the fimbria, stria terminalis, and stria medullaris. Significant Group×TimePoint interactions were also identified. Specifically, fw-F increased over time in both groups, with a greater increase in 3xTg-AD mice. In contrast, fw-FA progressively decreased in 3xTg-AD mice, whereas NonTg animals showed a slight increase over time. Cross-sectional analyses at each time point consistently demonstrated higher fw-F and lower fw-FA values in 3xTg-AD mice relative to NonTgs. The magnitude of fw-FA reductions increased longitudinally, with maximum t-values of 11.67, 13.09, and 13.53 at TP1, TP2, and TP3, respectively.

Conclusions: These findings indicate progressive extracellular remodeling and microstructural degeneration associated with AD pathology, with fw–corrected diffusion metrics providing high sensitivity to disease-related tissue changes. In particular, the divergent trajectories of fw-F and fw-FA highlight complementary processes of increasing extracellular water content and declining intrinsic white matter integrity in the 3xTg-AD model over time.

POSTER # 6

FURTHER EVALUATION OF PNA5 FOR THE TREATMENT OF COGNITIVE DEFICIT IN A PRE-CLINICAL MODEL OF PARKINSON'S DISEASE. Bernard K, Rautenberg J, Erickson DB, Zollar JN, Pombo EL, Corenblum M, Corenblum J, Hammer M, Hay M, Falk T, Madhavan L. University of Arizona; Arizona Alzheimer's Consortium.

Background: Clinical diagnosis of Parkinson's disease (PD) is based upon the presence of motor symptoms, but non-motor symptoms such as cognitive decline are a prominent feature. Currently, there are no treatments that can intervene in disease progression, nor satisfactorily address PD associated cognitive decline. We have evaluated a glycosylated Ang (1-7) analog (PNA5) that shows increased peptide stability and enhanced CNS penetration. We've previously demonstrated that PNA5 improves cognition in male Thy-1αSyn (hαSyn) mouse model after 2 months of treatment through reduction of microglia-mediated neuroinflammation (Bernard et al., Experimental Neurology, 2024). Although men are 1.5 time more likely to receive a PD diagnosis than females, it is important that potential treatments can have a generalizable effect.

Methods: The current study aims to 1) determine the smallest efficacious dose of PNA5, 2) expand the study to females and determine if PNA5 can also enhance cognition in female mice, and 3) study the transcriptional mechanisms underlying PNA5 action. For male mice we have applied PNA5 at the previously used 1 mg/kg (s.c.) dose, as well as 0.5 mg/kg, and have collected behavioral data prior to PNA5 treatment (~4 months of age), as well as after treatment to determine if PNA5 is acting to merely prevent cognitive decline or is reversing established deficit. Post-mortem brains were assessed via immunohistochemistry (n = 10/group), RNA Sequencing, and protein chemistry (n = 10/group). Additionally, we have tested PNA5 in a female cohort of animals using similar methods to determine if the cognitive benefit is sex specific.

Results: At 4 months of age male animals show a cognitive decline by way of a decrease in the spontaneous alteration of hαSyn animals relative to WT counterparts (63.7% compared to 53.6%, $p = 0.0082$). Using a nestlet shredding task to evaluate fine motor behavior we also observe a pronounced motor deficit at this time point (21.87 g shredded compared to 2.452 g for hαSyn mice, $p < 0.0001$). Animals treated with PNA5 had an increase in cognitive performance, however, measures of motor performance were unchanged. Pathway analysis of RNAseq data shows that the main pathways altered through PNA5 action include cytoskeletal remodeling and immune signaling. Female animals displayed a milder phenotype, with cognitive features not appearing until 6 months of age for the hαSyn animals. However, treatment with PNA5 prevented the development of cognitive decline, and provided a modest benefit to the motor symptoms as well.

Conclusions: We confirmed that PNA5 can reverse cognitive decline seen in male hαSyn animals. RNAseq and pathway analysis support the work indicating that this effect is due to a dampening of inflammation in the hippocampus. PNA5 also prevents cognitive decline and partially reverses motor disturbances in the female hαSyn mice which have a later developing and milder phenotype. These data indicate that the PNA5-mediated change to behavior is cognition specific.

POSTER # 7

REAL-WORLD LECANEMAB UTILIZATION AND OUTCOMES FROM INITIATION THROUGH MAINTENANCE THERAPY IN EARLY ALZHEIMER'S DISEASE: A MULTICENTER RETROSPECTIVE STUDY (LEADER). Berry B, Camargo C, Chabrashvili T, Cooper G, Frost N, Giles S, Leahy C, Rosenbloom M, Sabbagh M, Sadowski M, Schreiber C, Schulz P, Soria J, Tousi B, Weisman D, Adams C. Minneapolis Clinic of Neurology; University of Miami; SUNY Upstate Medical University; Norton Neuroscience Institute; University of Utah; Memory Treatment Centers; Memorial Healthcare Institute for Neuroscience; University of Washington; Barrow Neurological Institute; NYU Langone Health; Citizens Memorial Hospital; The McGovern Medical School of UTHealth - Houston; The Neuron Clinic; Cleveland Clinic; Abington Neurological Associates; Eisai Inc.; Arizona Alzheimer's Consortium.

Background: Lecanemab is indicated for patients with AD at the MCI or mild dementia stage. Real-world evidence describing treatment outcomes across initiation and beyond, including during maintenance dosing, remains limited. This updated analysis from LEADER expands prior reporting with a larger patient cohort and follow-up beyond 18 months. LEADER is among the first real-world datasets to characterize maintenance-phase lecanemab utilization, including both intravenous (IV) and at-home subcutaneous (SC) regimens.

Methods: LEADER is a multicenter, retrospective, real-world cohort study conducted across 15 geographically diverse US neurology practices. Sites abstracted deidentified medical chart data for patients who received ≥7 IV biweekly infusions. Maintenance cases were defined as patients with ≥3 months of maintenance therapy following initiation, including monthly-IV or weekly-SC dosing. Safety and clinical outcomes included change in disease stage from baseline to last follow-up visit based on clinician-reported observations. Descriptive statistics were generated using data collected through May 8, 2026.

Results: Of 432 patients included, 155 (35.9%) transitioned to monthly-IV maintenance, of whom 8 switched to weekly SC maintenance; 7 patients transitioned straight from monthly-IV maintenance to weekly SC maintenance. Mean age was 73.9 years; 55.8% were female; 90.5% of patients were White, and 13.0% were Hispanic or Latino origin. At baseline, 35.6% of patients had MCI due to AD and 64.4% had mild dementia due to AD; 77.8% currently or had previously received approved AD medications (e.g., donepezil and/or memantine). 66.7% of patients were APOE ε4 carriers (n=288), and 13.4% were homozygotes (n=58), with 2.8% (n=12) unknowns. Clinicians reported that 84.5% of patients were either stable (79.3%) or perceived as improved (5.2%; from mild AD dementia to MCI due to AD) over the observation period (mean treatment duration: 520.0 days; mean number of lecanemab doses: 25.7). ARIA occurred in 12.3% (n=53) of patients, including 6.5% of ARIA-E (n=28) and 7.6% of ARIA-H (n=33); 8 events were concurrent ARIA-E and ARIA-H. Adverse events led to treatment discontinuation in 7.4% of patients (n=32); 2.8% related to ARIA (n=12; ARIA-E: n=4; ARIA-H: n=5; ARIA-E and ARIA-H: n=3). Dose hold or missed infusions occurred due to ARIA in 3.0% of patients (treatment resumed). No macrohemorrhages or treatment-related deaths occurred.

Conclusions: In routine clinical practice, 84.5% of patients were reported as clinically stable or improved over the observation period, with a mean treatment duration of 17 months. Safety outcomes, including ARIA, were consistent with the known risk profile of lecanemab. Ongoing analyses of the full LEADER dataset will further characterize longer-term outcomes and safety in routine clinical practice.

POSTER # 8

CLUSTERING OF ALZHEIMER'S DISEASE-RELATED CEREBROSPINAL FLUID BIOMARKERS AND ITS RELATION TO COGNITIVE DECLINE IN HEALTHY OLDER ADULTS. Bharadwaj PK, Grilli MD, Chou Y, Andrews-Hanna JR, Raichlen DA, Alexander GE. University of Arizona; University of Southern California; Arizona Alzheimer's Consortium.

Background: Fluid biomarkers provide the opportunity to evaluate the presence of Alzheimer's disease (AD) brain pathology prior to the development of overt clinical symptoms, so disease-modifying treatments and prevention therapies can be implemented early. To support this effort, there is an urgent need to further operationalize the use of fluid biomarkers to help identify those at greatest risk for cognitive decline and dementia.

Methods: We implemented a hybrid clustering procedure which involved hierarchical and K-means clustering of automated cerebrospinal (CSF) fluid measures of phosphorylated Tau 181 (pTau181) and Beta-Amyloid (1-42), in conjunction with a consensus poll across a standard set of 23 quantitative clustering quality indices (Charrad et al., 2020; Erbacher, 2020) to identify subgroups within a sample of cognitively unimpaired (CU) participants drawn from the Alzheimer's Disease Neuroimaging Initiative (ADNI; n = 504, mean age = 72.5 ± 6.2 years, age range = 56 – 90 years, 56.7% female, education = 16.6 ± 2.5 years, Mini-Mental State Exam (MMSE) score = 29.1 ± 1.1). Cluster subgroup differences at baseline were evaluated using ANOVA models, and included demographics, clinical characteristics, cognitive function as measured by the modified preclinical AD cognitive composite (mPACC), the Clinical Dementia Rating scale - sum of boxes score (CDR-sb), composite measures of memory and executive function (PHC-Memory, PHC-EF), and structural MRI-derived measures of global brain, hippocampal, ventricular, and white matter hyperintensity (WMH) volumes. ANCOVA models with baseline age, sex, years of education, study site, history of hypertension, and apolipoprotein (APOE) carrier status as covariates were used to evaluate whether the two-year change scores for the cognitive function measures differed across cluster membership.

Results: The hybrid clustering procedure identified an optimal three cluster solution that contained 183 (cluster 1), 188 (cluster 2), and 133 (cluster 3) participants, respectively. Mean CSF Aβ42 was highest in cluster 1 (Mean ± S.D = 2000.5 ± 494.4 pg/mL), intermediate in cluster 2 (Mean ± S.D = 1139.7 ± 287.5 pg/mL), and lowest in cluster 3 (Mean ± S.D = 733.1 ± 232.9 pg/mL). CSF pTau181 was the highest in cluster 3 (Mean ± S.D = 29.5 ± 10.7 pg/mL), lowest in cluster 2 (Mean ± S.D = 14.1 ± 2.6 pg/mL), and intermediate in cluster 1 (Mean ± S.D = 22.9 ± 5.9 pg/mL). Participants in cluster 3 were significantly older (FDR-p = 1.19e-06), had the highest prevalence of APOE ε4 carriers (57.9%), larger WMH volumes (FDR-p ≤ 1.46E-03) than clusters 1 and 2, and larger ventricular volumes than cluster 1 (FDR-p ≤ 2.95E-06). Cluster 3 showed poorer performance than clusters 1 and 2 on PHC-EF and on PHC-Memory relative to cluster 2. On the mPACC-DSym and mPACC-TrailsB, the scores for cluster 3 were lower than cluster 2, but not different from cluster 1. Cluster 3 demonstrated greater two-year cognitive decline on CDR-sb ratings than both clusters 1 and 2 and on mPACC-TrailsB relative to cluster 1.

Conclusions: Model-free multivariate clustering of fluid biomarkers of AD applied to CU healthy older adults identified three subgroups that exhibited baseline differences in expression of AD risk factors, cognitive dysfunction, and structural brain volumes, as well as two-year cognitive declines. Clustering methods may help to identify early preclinical subgroups of individuals at greater risk for the subsequent development of AD. These findings provide support for an alternative framework for biomarker categorization in the context of preclinical AD that has the potential to identify those older adults who may especially benefit from early intervention to prevent cognitive decline and AD dementia.

POSTER # 9

SMAD2 SIGNALING REGULATES HIPPOCAMPAL MEMORY IN ADULT, AGING, AND APP/PS1 MICE. Bhuiyan P, Huckabee S, Judd J, Fritz M, Wright E, Keiser A. Arizona State University; Arizona Alzheimer's Consortium.

Background: Disruption of gene expression and synaptic plasticity, which are essential for memory formation, are associated with age-associated cognitive decline and Alzheimer's disease (AD). Phosphorylated SMAD2 (p-SMAD2), a key regulator of TGF-β signaling, is aberrantly retained in the cytoplasm rather than translocating to the nucleus in AD, suggesting disrupted SMAD2-dependent transcriptional regulation of memory-related genes. However, whether SMAD2 phosphorylation is both essential and sufficient for hippocampus-dependent memory in healthy contexts or whether enhancing SMAD2 phosphorylation can reverse cognitive function in aging and AD remains unexplored.

Methods: To address this question, we generated AAV1 vectors expressing phospho-mimetic Smad2 (S464D, S465D, S467D), phospho-null Smad2 (S464A, S465A, S467A), or control empty vector (EV) constructs. We confirmed the expression of these constructs by western blot analysis. To test whether disrupting endogenous SMAD2 phosphorylation is required for hippocampal memory formation, phospho-null Smad2 (S464A, S465A, S467A) or EV were expressed through stereotaxic viral delivery into CA1 region of hippocampus in 3-month-old C57BL6 mice. To determine whether enhancing SMAD2 phosphorylation improves memory function, phospho-mimetic Smad2 (S464D, S465D, S467D) were overexpressed in the hippocampal CA1 region of 20-month-old C57BL6, as well as 13-month-old 129S6 SvEv and APP/PS1 male and female mice. Hippocampus-dependent memory was assessed utilizing Object Location Memory (OLM) task.

Results: Phospho-null Smad2 significantly impaired OLM performance relative to controls, confirming that intact p-SMAD2 signaling is required for normal hippocampal memory formation. In 20-month-old senescent C57BL/6 mice, phospho-mimic SMAD2 significantly improved performance in the OLM compared to age-matched controls. Similarly, phospho-Smad2 over-expression significantly enhanced OLM performance in both 129S6/SvEv wild-type and APP/PS1 transgenic mice compared with EV mice, indicating that SMAD2 phosphorylation is sufficient to counteract amyloid-driven cognitive decline. In separate cohorts, subcellular fractionation was conducted to evaluate the localization of p-SMAD2 in cytoplasmic and nuclear fractions during the 1-hour memory consolidation window. Mechanistically, phospho-mimetic Smad2 increased nuclear localization of p-SMAD2 during memory consolidation, consistent with canonical nuclear SMAD2 transcriptional signaling.

Conclusions: Together, these findings identify SMAD2 signaling as a functional regulator for hippocampus-dependent memory with potential therapeutic strategy for age-related memory decline and AD.

POSTER # 10

BLOOD PRESSURE, SERIOUS LIFE EVENTS, AND COGNITIVE AGING AMONG OLDER BLACK AMERICANS IN THE HEALTH ABC STUDY. Byrd DR. Arizona State University; Arizona Alzheimer's Consortium.

Background: High blood pressure is a well-documented risk factor for cognitive decline, yet the role of stressful life events in modifying this relationship remains underexplored, particularly among Black Americans. This study examined whether high blood pressure predicts changes in cognitive functioning over time and whether stressful life events moderate this relationship. It is critical to understand the psychosocial factors that may buffer this association, as Black Americans are disproportionately affected by both hypertension and cognitive decline.

Methods: Data were derived from 770 Black Americans (aged 68–95) in The Dynamics of Health, Aging, and Body Composition Study (Health ABC), with data collection conducted over 11-years. Cognition was assessed using the Digit Symbol Substitution Test (DSST) and measured at baseline and at follow-up years 5, 8, 10 and 11. Objective blood pressure (BP) measures of systolic and diastolic were taken. Participants were asked if they had experienced any of 7 serious life events in the past year (yes/no response). Sample items include "serious accident or illness in a close friend or family member; death of a partner/spouse; child, grandchild, close friend, or relative." Possible number of negative life events ranged from 0 (none) to 7 (all events). This variable was categorized as 0,1, 2 and 3 or more life events. Data were analyzed using mixed effects models, controlling for covariates.

Results: Findings revealed no direct association between BP and follow-up cognitive changes. We fit a linear mixed model to account for the longitudinal structure of the data, treating participants as a random effect. Although the omnibus fixed interaction between serious life events (SLE) and diastolic BP did not reach significance, chi2(7) = 10.10, Prob > chi2 = 0.183, we decomposed the interaction to examine the simple slopes for each categorical level of SLE. This analysis revealed that the relationship between DBP and the outcome was non-significant for most groups (all p's>.05) but was statistically significant specifically within the individuals reporting 3 or more SLE group (b= .105,SE= .054,z= 1.96,p=.05).

Conclusions: These counterintuitive findings suggest that serious life events are a modifiable factor that can contribute to better cognition even with high blood pressure. This finding is limited to a small number of participants and warrants future study. Our study was limited in using a single cognitive measure. Black Americans are at higher risk for hypertension-related health disparities. Future research should continue to explore the role of serious life events in the BP-cognition relationship as these are preliminary findings that require further investigation.

POSTER # 11

DEVELOPMENT AND INITIAL IMPLEMENTATION OF A PRECISION BRAIN HEALTH PATHWAY FOR COGNITIVELY UNIMPAIRED ADULTS IN THE ALZHEIMER'S BLOOD BIOMARKER ERA. Cabral D, Joslin M, Mahan A, Hunt Brendish K. BrainLove; University of Arizona College of Medicine – Phoenix; Desert Rose Neuropsychology; Arizona State University; Arizona Alzheimer's Consortium.

Background: The emergence of Alzheimer's blood biomarkers is transforming brain health care among cognitively unimpaired adults by enabling increasingly personalized assessment of Alzheimer's disease risk and creating new demand for individualized evaluation and care planning. Existing clinical models have largely been designed to diagnose and manage symptomatic cognitive disorders rather than translate complex brain health information into personalized strategies and actionable recommendations. Biomarker disclosure alone may not be sufficient to promote sustain behavior change highlighting the need for structured clinical pathways that support responsible risk communication, patient activation, and evidence-based risk reduction.

Methods: A structured precision brain health clinical care pathway was developed through synthesis of the Alzheimer's biomarker disclosure literature, evidence supporting Alzheimer's risk reduction, emerging brain health concepts, and multidisciplinary expert clinical guidance. The pathway will be evaluated in a prospective pilot study of cognitively unimpaired adults 50 years or older presenting for a precision brain health evaluation within a specialty cognitive care practice. Participants will be enrolled sequentially and structured measures will evaluate feasibility, acceptability, and psychological safety along with preliminary data describing individualized behavior change.

Results: The resulting pathway addresses the gap between increasingly personalized Alzheimer's disease risk assessment and effective implementation of individualized, evidence-based action. The pathway follows a sequential process of (1) Assessment, (2) Interpretation, (3) Prioritization, (4) Action, (5) Support, and (6) Adaptation, integrating biological, genetic, neuropsychological, medical, lifestyle, and patient-centered information to identify individualized opportunities for intervention and prioritize recommendations with longitudinal support. Descriptive demographics will be collected. Feasibility and acceptability measures will capture enrollment rate, retention, time to complete pathway, and satisfaction ratings. Psychological safety measures include the Hamilton Depression Rating Scale, State-Trait Anxiety Inventory, the Columbia Suicide Severity Rating Scale, and the Impact of Event Scale – Revised. Achievement of personally meaningful brain health goals will be assessed using Goal Attainment Scaling in real-world clinical practice.

Conclusions: As Alzheimer's biomarker testing becomes increasingly accessible and secondary prevention therapies advance through clinical development, practical care pathways are needed to support responsible and effective precision brain health care. This pathway establishes a structured clinical model for evaluating how personalized risk information can be translated into meaningful action, identifying which components of assessment, communication, prioritization, and longitudinal support provide the greatest value. Prospective evaluation and iterative refinement will inform scalable, personalized, and patient-centered approaches to brain health care.

POSTER # 12

IDENTIFICATION OF NOVEL MARKERS OF AMYLOID PLAQUES AND CEREBRAL AMYLOID ANGIOPATHY IN ALZHEIMER'S DISEASE USING LASER CAPTURE MICROSCOPY. Cadiz MP, Nascari DG, Leka K, Sharma R, Pirrotte P, Fryer JD. Translational Genomics Research Institute; Mayo Clinic Arizona; Integrated Mass Spectrometry Shared Resource, City of Hope Comprehensive Cancer Center; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by extracellular amyloid beta and intracellular tau. Amyloid plaques, which deposit in the parenchyma, are neurotoxic and trigger local inflammation in the surrounding tissue. In the majority of AD patients, amyloid also deposits in the vessels of the brain, a condition known as cerebral amyloid angiopathy (CAA). Amyloid-laden vessels are more susceptible to bleeding and inflammation (CAA-ri), which increase the risk of stroke and microhemorrhage. We sought to identify protein signatures shared between both compartments, and specific to plaques and CAA.

Methods: 50-micron sections from the Tg2576 amyloidosis mouse model were stained free-floating with anti-smooth muscle actin to mark vessels, and Thio-S to mark amyloid beta, and mounted onto PEN frame slides. Slides were imaged on a Keyence microscope and images were analyzed in QuPath. The following regions were identified and manually annotated: plaques, parenchyma without plaques, CAA, and vessels without CAA. A custom script was used to export shapes in an .xml file for cutting on the Leica LMD7 laser microdissection microscope. Cut samples were rehydrated in ACN, dried, then boiled in a DDM and TEAB based lysis buffer at 95°C for 1 hour and 75°C for another hour. Overnight digestion was performed with 1ng lys-C and 3ng Trypsin. Samples were cleaned and injected using the EvoSep System using DDM loading solvent. MS data were acquired on Evosep One liquid chromatography system coupled to a Bruker timsTOF Ultra mass spectrometer. Samples were searched in Spectronaut (v20.3) in directDIA mode against mouse protein fasta with default settings. Protein abundances were normalized using variance stabilization normalization (VSN) in R v4.4.0.

Results: We identified a total of 9,384 proteins across 20 samples (average = 7,027), including 4,550 proteins from a single plaque of area 682 micron squared. A core amyloid signature consisting of 146 proteins differentially abundant ($p<0.05$) in both plaques vs. parenchyma, and CAA vs. vessels, included canonical co-aggregates (CLU, APOE) and markers of gliosis (GFAP, C1QC). Intriguingly, 79 proteins displayed opposite enrichment across compartments, such as ATP8A1 and PTPRN2 (enriched in plaques but depleted in CAA), and AEBP1 and KCNAB3 (enriched in CAA but depleted in plaques). We additionally identified a set of proteins that are either significantly upregulated or selectively detected in each amyloid compartment.

Conclusions: Laser capture microscopy of plaques and CAA enabled the identification of shared and distinct amyloid signatures across plaques and CAA, and nomination of candidate biomarkers. Our ongoing work is focused on elucidating the plaque- and CAA-specific proteome in human APOE3/3 and APOE4/4 samples.

POSTER # 13

A DOMAIN-AWARE LONGITUDINAL DEEP LEARNING ARCHITECTURE FOR MULTIMODAL PREDICTION OF COGNITIVE DECLINE AND DIAGNOSTIC PROGRESSION.

Chen K, Belden C, Choudhury P, Arch A, Arce R, Beach T, Serrano G, Atri A. Banner Alzheimer's Institute; Arizona State University; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Longitudinal prediction of cognitive decline and diagnostic progression from multimodal biomedical data remains challenging because different feature domains have distinct temporal patterns, missing data, and variable follow-up. Conventional LSTM typically concatenate all predictors into a single sequence, limiting their ability to capture domain-specific temporal information and reducing interpretability.

Methods: We developed and evaluated two longitudinal deep learning models using multimodal data from 2,161 participants (10,114 visits) in the Banner BBDP. Model A used a single LSTM encoder for all predictors, whereas Model B employed domain-specific LSTM encoders (demographic, cognitive, imaging, biomarker, genetic, and clinical) followed by multimodal feature fusion. Both supported variable-length longitudinal data, missing observations, simultaneous regression and classification, optimized decision thresholds, and GPU acceleration. Performance was evaluated with 10-fold CV.

Results: Both models achieved robust longitudinal cognitive prediction and diagnosis. Model A attained 86.9% overall classification accuracy (72.3% sensitivity, 93.6% specificity), with per-visit accuracies of 84.5%–93.0%. Model B achieved comparable performance while improving interpretability through domain-specific temporal representations. The most influential predictors included AVLT long-term percent recall, baseline age, visit time, Trail Making Test Part B, and Stroop Word performance.

Conclusions: A domain-aware longitudinal LSTM provides a more interpretable alternative to conventional single-stream models while maintaining predictive performance. The framework supports heterogeneous multimodal longitudinal data and offers a scalable approach for neurodegenerative disease research.

POSTER # 14

EXPLORATION OF ADVANCED DIFFUSION Q-SPACE TRAJECTORY IMAGING IN AGING EX. VIVO BONNET MACAQUE BRAINS. Comrie CJ, Dieckhaus L, Barnes C, Hutchinson EB. University of Arizona; Arizona Alzheimer's Consortium.

Background: Traditional single diffusion encoding frameworks have been investigated for their unique ability to provide insight into the microstructural environments of nervous tissue. Despite the diagnostic potential of SDE frameworks, they are accompanied with innate limitations. Traditional diffusion frameworks rely on probing single points within q-space to measure the diffusivity within a single voxel. Resulting in time-intensive acquisitions, strong gradient hardware needs, and computational demands with complex post-processing methodologies. Q-space trajectory imaging (QTI) has emerged in recent years as an alternative diffusion MRI (dMRI) acquisition. QTI acquisitions allow for timely differentiation of geometric features during acquisition, setting it apart from traditional SDE frameworks. Without requiring extensive DWIs and post-processing to infer these microstructural shapes, QTI depends on continuous waveforms specifically designed to probe linear, planar, or spherical shapes directly from the tissue microstructure during acquisition.

Methods: Bonnet macaque brains (age 14-30 years) prepared by the Carol Barnes laboratory, underwent a transcardial perfusion, a 4% Paraformaldehyde immersion fixation, and stored in a phosphate buffered saline solution with 0.1% sodium azide. In preparation for imaging, bonnet macaque specimens were prepped with gauze for support and submerged and vacuum sealed in non-protonated fluid fluorinert (FC-3823, 3M, St. Paul, MN). All MR imaging was performed on a 7T Bruker Biospec scanner. The QTI acquisition included three different waveforms with timings of 21-22-21 for linear (LTE), planar (PTE), and spherical tensor encoding (STE) shapes. Multi-shell diffusion encoding used the following scheme for shapes LTE and PTE b(# directions) = 0, 500(6), 1000(12), 2000(12), and 4000(32) s/mm2. While STE used b = 125, 500, 1000, 2000, 4000 for 6 directions. MDM mapping was done with the DIPY library in python, and produced mean diffusion (MD), fractional anisotropy (FA), and micro-anisotropy (uFA). Additionally, the final shell b=4000 s/mm2 was averaged into the 4000/A0 metric for PTE and STE shapes.

Results: Inspection of the PTE/A0 map shows brightening and contrast of the planar sheets within white matter. Additionally, the sub-nuclei of the thalamus (mediodorsal) within PTE/A0, STE/A0, FA, and uFA maps display striking and bright contrast across all ages but is especially pronounced in the younger specimens.

Conclusions: QTI is a promising prospect in understanding differences of microstructural changes that occur during aging and neurodegenerative disease. Allowing for more selective probing of the microstructural shapes and cellular structures through waveform design and MR sequence encoding. Qualitative analysis displays striking hyperintensities within the thalamus, and future region of interest analysis hopes to uncover potential aging relationships with QTI.

POSTER # 15

CEREBELLAR CALCIUM BINDING AND PERINEURONAL NET DYSFUNCTION IN YOUNG INDIVIDUALS WITH AUTISM SPECTRUM DISORDER. Craig M, Schafernak K, Mufson E, Perez S. Barrow Neurological Institute; Phoenix Children's; Arizona Alzheimer's Consortium.

Background: Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder characterized by deficits in social communication and social interaction, as well as restricted interests and repetitive patterns of behavior. Abnormalities in calcium-binding proteins associated with inhibitory neuronal systems and perineuronal nets (PNNs), specialized extracellular matrix structures involved in synaptic plasticity, may contribute to ASD. While much of the existing literature has focused on abnormalities in neuronal plasticity within cortical regions, the role of the cerebellum, a brain structure involved in motor coordination, cognition, and social behavior, remains understudied in ASD.

Methods: Here, we qualitatively and quantitatively examined the astrocytic calcium-binding proteins calbindin (Calb), parvalbumin (Parv), and S100B; the astrocytic inflammatory marker GFAP; and the PNN components aggrecan and brevican in immersion-fixed postmortem cerebellar tissue obtained from children and young adults (1-21 years of age) with ASD or at high risk of developing ASD, as well as age-matched neurotypical controls (NCD), using immunohistochemistry and densitometry. Cerebellar aggrecan and brevican expression were also examined in NCD cases at postnatal ages ranging from 7 days to 8 months.

Results: Brevican and aggrecan immunostaining was observed within Purkinje cells (PCs), as well as within synaptic islands in the granular cell layer and white matter across all ages in both ASD and NCD cases. No significant differences were observed between groups in the density of Calb-, Parv-, S100B-, or GFAP-immunoreactive cells, nor in aggrecan and brevican optical density (OD) values across the cerebellar layers examined. However, brevican OD values in the granular cell layer were significantly higher than aggrecan OD values in ASD cases, whereas no such difference was observed in NCD cases. A significant negative correlation was found between the number of Parv-immunoreactive PCs and aggrecan OD values in the granular cell layer in ASD. In contrast, positive correlations were observed between brevican and aggrecan OD values in PCs, white matter, and the granular cell layer in ASD. Brevican OD values in PCs were negatively correlated with age in ASD but not in NCD cases.

Conclusions: Collectively, these findings suggest that increased aggrecan and brevican expression during postnatal development and throughout early adulthood affect synaptic plasticity within the cerebellum that may contribute to cognitive, social, and motor deficits associated with ASD.

POSTER # 16

CONTRIBUTION OF ASTROCYTIC SPARCL1 TO CORTICAL SYNAPTIC DYSFUNCTION IN C9ORF72-FTD/ALS. Culibrk RA, Gittings LM, Bustos LM, Ondatje B, Julian D, Hansen NP, Sharma R, Alsop EB, Antone J, Van Keuren-Jensen K, Pirrotte P, Sattler R. Barrow Neurological Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Recent studies suggest that altered astrocyte secretion of synaptogenic factors affects cortical neuronal viability and is a central driver of synaptic dysfunction in various neurodegenerative diseases. We previously demonstrated that one such factor, Sparcl1, is significantly reduced at the mRNA and protein levels in C9orf72-FTD/ALS (C9) postmortem frontal cortex tissues and patient iPSC-derived cortical astrocytes, respectively. Herein, we aim to assess (1) the impact of SPARCL1 knockdown on human cortical astrocyte viability and function and (2) the electrophysiological consequences of modulating Sparcl1 levels within a human neuron-astrocyte coculture system.

Methods: Human primary cortical astrocytes (hCA) were stably transduced with doxycycline-inducible non-targeting or SPARCL1 shRNA. Following, Day 3 i3Neuron progenitor cells (9x10^4/well), with or without hCA (4.5x10^4/well), were spot-seeded into 48-well multielectrode array plates (n = 6-7). Separately, Day 21 i3Neuron monocultures received 10 or 100 nM recombinant human Sparcl1 (rhSparcl1) continuously during biweekly medium changes. Electrophysiological activity was recorded using the Axion Maestro system, and excitatory synaptic puncta colocalization (vGlut1/Homer1) was quantified using SynQuant.

Results: Continuous rhSparcl1 administration significantly increased the weighted mean firing rate (wMFR) and vGlut1/Homer1 colocalization of i3Neuron monocultures in a dose-dependent manner ($p < 0.05$), suggesting Sparcl1 is sufficient to drive excitatory synaptic maturation without direct astrocytic contact or astrocyte-derived trophic factors. Conversely, shRNA-mediated depletion of astrocytic SPARCL1 significantly attenuated the ability of hCA to support long-term firing in i3Neuron-hCA cocultures (~5-fold, $p < 0.05$), implicating Sparcl1 as a critical effector of synaptic potentiation. Finally, SPARCL1 knockdown in hCA significantly altered cellular morphology, increased cytotoxicity measured via LDH, decreased glutamate uptake capacity, and altered the expression of multiple mRNAs associated with astrocyte reactivity and function.

Conclusions: Collectively, these findings suggest a crucial, cell autonomous requirement for astrocytic Sparcl1 in maintaining cytoskeletal integrity, metabolic viability, and glutamate homeostasis. They additionally support a critical role for Sparcl1 in excitatory synaptic development and maintenance and conversely suggest that its loss in C9 may contribute to astrocytic dysfunction, cortical synaptic degeneration, and neuron death. Our ongoing work extends these characterizations to control and C9 patient iPSC-derived neuron-astrocyte coculture systems.

POSTER # 17

RELATIONSHIP BETWEEN P-TAU217, COGNITION, AND PET IMAGING IN THE ARIZONA ADRC. Edmonds EC, Siu H, Traslavina Jimenez J, Grilli MD, Rapcsak SZ. Banner Alzheimer's Institute – Tucson; University of Arizona; Arizona Alzheimer's Consortium.

Background: Plasma p-tau217 has good sensitivity and specificity for detecting Alzheimer's disease (AD) pathology, but previous work shows that it may not provide information about clinical relevance or stage. We examined the relationship between p-tau217, cognition, and amyloid and tau PET imaging in the Arizona Alzheimer's Disease Research Center (ADRC) cohort.

Methods: 507 participants (mean age=74.7 years; mean education=15.9 years; 61% female; 78% non-Hispanic white) from the Arizona ADRC completed p-tau217 testing and neuropsychological assessment. Consensus diagnoses included normal cognition (n=369), impaired-not-MCI (n=15), MCI (n=76), and dementia (n=47). A subset of the sample (n=86) also had amyloid and tau PET scans available. We examined correlations between p-tau217 level, neuropsychological test scores, amyloid PET Centiloids, and tau PET SUVRs. Area under the curve (AUC) analysis examined the ability of p-tau217 to predict amyloid and tau PET status.

Results: Mean p-tau217 levels were significantly higher in participants with MCI and dementia (0.76-0.78 pg/mL) compared to normal cognition and impaired-not-MCI (0.45-0.48 pg/mL; $p<.001$). After controlling for demographic variables, p-tau217 level was negatively correlated with tests of global cognition, memory, language, attention, and executive functioning. Importantly, in cognitively impaired participants (MCI/dementia), p-tau217 was specifically related to the cognitive domains typically affected in AD (i.e., episodic memory and semantic memory/language). In the full sample, there were significant positive correlations between p-tau217 level and amyloid PET Centiloid scores ($r=.557$) and tau PET SUVRs in entorhinal ($r=.634$) and meta-temporal ($r=.600$) ROIs (all $p<.001$). The correlations between p-tau217 and entorhinal and meta-temporal tau SUVRs remained significant after controlling for the association between p-tau217 and amyloid PET lesion burden ($r = .423$ to $.445$, $p<.001$). Furthermore, p-tau217 performed well in a binary classification model predicting amyloid and tau PET status with AUCs ranging from .747 to .827. Additionally, episodic and semantic memory measures were both correlated with amyloid PET Centiloids and tau PET SUVRs.

Conclusions: Findings suggest that p-tau217 is predictive of clinically symptomatic cognitive impairment with an AD neuropsychological profile. However, p-tau217 does not distinguish clinical stage (i.e., MCI vs. dementia), highlighting the value of integrating neuropsychological and biomarker data. Consistent with the literature, results in our Arizona ADRC cohort suggest that p-tau217 may be used not only to detect AD pathology (Core 1 biomarker) but also to provide information about the topography (Braak stage) and magnitude of tau lesion burden important for biological staging (Core 2 biomarker) and closely related to cognitive impairment.

POSTER # 18

A NON-INFERIORITY EVALUATION OF DIGITIAL DISCLOSURE: A SCALABLE ALTERNATIVE FOR RETURNING ALZHEIMER'S GENETIC AND BIOMARKER RESULTS.

Erickson C, Langlois C, McCarty Wood B, Egleston B, Harkins K, Mim R, John S, Ofidis D, Enos J, Salata H, DeSantiago D, Largent E, Reiman EM, Denkinger MN, Ashton NJ, Roberts S, Karlawish J, Bradbury A, Langbaum JB. Banner Alzheimer's Institute; University of Pennsylvania; Fox Chase Cancer Center; Banner Sun Health Research Institute; University of Michigan School of Public Health; Arizona Alzheimer's Consortium.

Background: Blood biomarkers (BBM) and genetic testing are poised to transform Alzheimer's disease (AD) risk assessment, particularly with anticipated broader clinical adoption of plasma pTau-217 assays alongside *APOE* genotyping. At the same time, due to the 21st Century Cures Act, patients in the U.S. are increasingly learning AD-related test results through electronic health portals. Together, the confluence of demand for AD-related testing, shortage of genetic counselors and dementia specialists, and healthcare policy which generally requires immediate return of medical test results, heighten the need to identify alternative scalable delivery models of AD risk information that are safe, comprehensible, and also minimize healthcare system burden.

Methods: The Evaluation of Self-mediated Alternatives for Risk Testing Education and Return of results (eSMARTER) study is a randomized, non-inferiority clinical trial to evaluate self-directed digital interventions for returning *APOE* (primary) and pTau-217 results (exploratory) to adults aged 60–80 years. After consent, the baseline survey, and optional digital education, participants were randomized 2:1 to digital or clinician-mediated telehealth return of results. *APOE* return of results occurred first. Patient-reported outcomes (PROs) were collected at baseline (T0), 2-7 days (T1), 6 weeks (T2), and 6 months (T3) following *APOE* disclosure. After T3, participants had the option to learn their pTau-217 result. Plasma p-Tau217 concentrations were measured on the Roche cobas e801 platform using a Research Use Only (RUO) assay. Thresholds were developed resulting in three stratification levels: negative, intermediate, and positive. PROs were collected 2-7 days (T4), and 4 weeks (T5) after return of pTau-217 results. The three primary non-inferiority outcomes were changes in anxiety, genetic knowledge, and disease-specific distress (T0-T1). Non-inferiority was concluded if the upper bound of the 96.7% confidence interval did not cross the pre-defined non-inferiority threshold in a direction that would favor clinician-mediated return of results.

Results: Results: 674 persons (mean [SD] age 68 [4.7] years; 451 [67%] female; mean [SD] telephone MoCA=19 [2]) were eligible and provided demographic information. 651 participants were randomized to clinician-mediated (n=216) or digital disclosure (n=435) and completed APOE disclosure (66 [10%] *APOE4* homozygotes, 377 [58%] heterozygotes, 208 [32%] non-carriers). Baseline characteristics were balanced across groups. 604 participants completed the study; 500 completed optional pTau-217 disclosure. pTau-217 results were: 47% negative, 31% intermediate, and 22% positive. At 1-7 days following *APOE* disclosure, scores on AD-related knowledge, PROMIS Anxiety, and disease-specific distress measures met non-inferiority. Non-inferiority was also met for these outcomes at T0-T2 and T0-T3. For pTau-217 disclosure, comparisons between the digital and clinician-mediated arms did not reach significance on measures of BBM knowledge at T4 (p=0.58) and T5 (p=0.80), T3-T4 change in anxiety (p=0.79) or disease-specific distress (p=0.07), and T3-T5 change in anxiety (p=0.31) or disease-specific distress (p=0.74). Analyses of other secondary PROs and moderator analyses are ongoing.

Conclusions: Disclosure of *APOE* genotype by the eSMARTER digital platform is non-inferior to clinician-mediated telehealth disclosure. No significant between group differences were found following disclosure of pTau-217 results. Together, these results suggest that this digital platform may provide an evidence-based scalable approach for returning AD genetic and biomarker results.

POSTER # 19

AMBIENT AIR CONCENTRATIONS OF TOXICANTS AND RISK OF ALZHEIMER'S DISEASE.
Faust IM, Shivani Chirag S, Racette BA. Barrow Neurological Institute; Washington University School of Medicine; University of The Witwatersrand; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by memory loss, cognitive decline and behavioral changes. Though genetic factors play a role in disease development, multiple studies have demonstrated that exposure to air pollution in the form of particulate matter <2.5 microns is associated with AD risk. Whether other neurotoxicants contribute to AD risk is relatively understudied.

Methods: We conducted an in silico exposomics study to investigate the risk of AD in relation to ambient air toxicants in a population-based study of 52,629 incident AD cases and 263,145 controls from Medicare claims data from 2016-2018. Estimated exposures were obtained for 175 ambient air toxicants from the Environmental Protection Agency's 2014 National Air Toxics Assessment (NATA), a nationwide record of toxic air emissions. We linked these exposures to each beneficiary's residential ZIP+4. We used logistic regression to calculate the odds ratio (OR) and 95% confidence intervals (CI) for each toxicant, adjusting for age, sex, and race. Significant associations were determined using the Bonferroni correction for multiple comparisons.

Results: Of the 175 NATA ambient air toxicants, 20 were associated with AD risk after correcting for multiple comparisons. The strongest associations were formaldehyde (OR 1.09, 95% CI 1.07-1.10), acetaldehyde (OR 1.07, 95% CI 1.06-1.08), methanol (OR 1.06, 95% CI 1.05-1.07) and acrolein (OR 1.05, 95% CI 1.04-1.06).

Conclusions: Exposure to specific ambient air toxicants may increase the risk of AD.

POSTER # 20

THE EFFECTS OF OLDER AGE AND DEPRESSION ON EVERYDAY AUTOBIOGRAPHICAL THINKING. Garcia A, Grilli M, Andrews-Hanna J. University of Arizona; Arizona Alzheimer's Consortium.

Background: Older adults have a general tendency towards positivity in their thoughts and memories. However, whether depression weakens the positivity effect in older adults' everyday autobiographical thoughts remains unclear.

Methods: The present preregistered study compared how cognitively unimpaired older adults (N = 150) and young adults (N = 61) describe their most frequently occurring thoughts from the past month. In addition to completing a self-report questionnaire for each thought, participants also reported their current depressive symptoms using the Center for Epidemiologic Studies-Depression Scale (CES-D).

Results: Results indicate that higher depressive symptomatology was associated with experiencing frequent everyday thoughts that are more negative in valence (B= -0.0494, p= <0.001) and more past-centered (B= -0.0348, p= <0.001). These results held when we restricted the analyses to older adults only.

Conclusions: Overall, these findings suggest that depressive symptoms may shape everyday autobiographical thinking by imbuing the most frequently occurring thoughts with more negative tone, and situating these thoughts generally in the past, rather than in the present or future.

POSTER # 21

SITE-SPECIFIC TAU ACETYLATION ALTERS MITOCHONDRIAL HOMEOSTASIS. Garcia CA, Hernandez B, Cristofono J, Tzeng J, Tseng JH. Arizona State University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is characterized by the accumulation of neurofibrillary tangles composed of aggregated tau protein. In AD, tau undergoes numerous post-translational modifications (PTMs) that contribute to its pathological properties. While tau phosphorylation has been extensively studied, other disease relevant PTMs remain comparatively unexplored. Among these, tau acetylation has emerged as an early pathological event associated with AD progression. Mitochondria dysfunction is also an early hallmark of AD, and pathological tau has been implicated in disrupting mitochondrial homeostasis. However, the contributions of tau acetylation to mitochondrial dysfunction remains unclear.

Methods: This study investigated the relationship between acetylated tau and mitochondrial dynamics. HEK cells were transfected with plasmids expressing full-length wild-type tau, the familial tau mutation P301L, or the acetylation mimic mutants K280Q and K311Q. Parallel experiments were conducted in primary mouse neurons derived from tau knockout mice, which were transduced with lentiviral vectors expressing either wild-type tau, P301L, K280Q, or K311Q. Changes in mitochondrial dynamics proteins, key regulators of mitochondrial fission and fusion, were assessed by western blotting analysis of whole cell lysates and isolated mitochondrial fractions. The effects of acetylated tau on mitochondria function were further evaluated using ATP and TMRM assays to assess cellular bioenergetics and mitochondrial membrane potential respectively, as well as confocal microscopy to examine alterations in mitochondrial morphology and network organization.

Results: Expression of acetylation-mimic tau mutants altered the levels of mitochondrial dynamic proteins in both HEK293 cells and primary cortical neurons. Similar changes were observed in neurons expressing diseased-associated tau variants, suggesting that pathological forms of tau disrupt pathways regulating mitochondrial fission and fusion. Notably, ATP levels were reduced in both HEK293 cells and primary neurons expressing the K311Q acetylation mimic, whereas K280Q had no detectable effect, indicating a site-specific impact of tau acetylation on mitochondrial function. In addition, disease-associated tau variants altered mitochondrial membrane potential in HEK293 cells, further supporting a role for pathological tau in mitochondrial dysfunction.

Conclusions: These findings support a role for site-specific tau acetylation in regulating mitochondrial homeostasis and provide insight into mechanisms linking pathological tau to mitochondrial dysfunction in AD. Ongoing studies are examining the effects of acetylated tau on mitochondrial turnover and associated neuronal dysfunction.

POSTER # 22

REPURPOSING THE FDA-APPROVED A-GLUCOSIDASE INHIBITOR MIGLITOL FOR ALZHEIMER'S DISEASE: EFFECTS IN APOE3/E4 BRAIN ORGANOIDS AND 3XTG-AD MICE.
Gendron W, Feng L, Winslow W, Umaiyalan VR, Gaikwad R, Chan Y, Wang Q, Lim ET, Velazquez Jr. R. Arizona State University; University of Massachusetts Chan Medical School; Arizona Alzheimer's Consortium.

Background: Efforts to repurpose FDA-approved therapies have emerged as a strategy to find alternative disease-modifying treatments for AD. We recently identified the diabetics drug target α-glucosidase MGAM as a novel drug repurposing target for AD. Miglitol (MIG), an MGAM inhibitor, may provide neuroprotective benefits by restoring systemic metabolic balance. Individuals carrying the APOE4 allele are at a higher risk for developing AD and are vulnerable to metabolic and inflammatory stressors. Targeting peripheral physiology is a promising therapeutic strategy because systemic metabolic dysfunction often precedes and accelerates AD pathology. We therefore investigated whether MIG reduces AD-related neuropathological and inflammatory markers in APOE33 (E33) vs E44 (E44) human AD brain organoids and in 3xTg-AD mice.

Methods: We differentiated 7-month-old 2D dissociated cells from cerebral organoids (dcOrgs) using induced pluripotent stem cells from E33 or E44 donors. 200uM of MIG treatment was introduced to mock dcOrgs or herpes simplex virus 1 (HSV-1) infected dcOrgs that model neuroinflammation associated with AD in-vitro. These samples were RNA sequenced. In parallel, at 7.5 months of age, 3xTg-AD mice received oral administration of vehicle, 10 or 30 mg/kg of MIG for 30 consecutive days (n = 3–4 per group; sex-balanced cohorts). We used Enzyme-linked immunosorbent assays to quantify plasma glial fibrillary acidic protein (GFAP), a marker of neuroinflammation, neurofilament light chain (NfL), a marker of neuroaxonal injury, and AD–related pathological markers, including soluble (sol) and insoluble (insol) Aβ40 and Aβ42 and phosphorylated tau (pTau Serine (S) 396, Threonine (T)231, and T217).

Results: MIG treatment on HSV-1-infected dcOrgs had significantly more differentially expressed genes (DEGs) in E33 compared to E44. Several MGAM downstream target genes were solely rescued in MIG-treated and infected E33 dcOrgs. No differences in DEGs were seen between MIG treated mock E44 and E33 dcOrgs, indicating that the effects of MIG occur only in HSV-1-infected dcOrgs. MIG treatment at 30 mg/kg was the most effective at decreasing sol and insol Aβ40 and Aβ42 in 3xTg-AD mice. In females, 30 mg/kg MIG reduced sol and insol pTau T217, as well as insol T231 and S396. At 30 mg/kg, males showed a reduction in insol S396. GFAP and NfL were significantly reduced with treatment, highlighting blood-based biomarker tracking to monitor treatment-associated changes.

Conclusions: These findings support the repurposing of MIG as a strategy for AD that may confer meaningful neuroprotective effects in the degenerating brain.

POSTER # 23

COMPARING BRAIN-DERIVED AND TOTAL PLASMA PTAU217 IN THE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE. Ghisays V, Denkinger MN, Singh A, Marques T, Malek-Ahmadi M, Van-Keuren Jensen K, Protas H, Sohankar J, Goradia D, Devadas V, Su Y, Weiner M, Reiman EM, Ashton NJ for The Alzheimer's Disease Neuroimaging Initiative. Banner Alzheimer's Institute; Banner Sun Health Research Institute; Translational Genomics Research Institute; University of California, San Francisco; Arizona Alzheimer's Consortium.

Background: Blood-based phosphorylated tau (p-tau) biomarkers have emerged as leading candidates for the detection and monitoring of Alzheimer's disease (AD). Recent assay developments now enable selective quantification of brain-derived (BD) pTau217 in blood, which may offer greater specificity for AD-related tau pathology than measurements of total circulating pTau217. Here, we compared BD and total p-tau epitopes, in the ADNI cohort.

Methods: Plasma samples from ADNI1/GO/2/3 participants spanning cognitively unimpaired (CU), mild cognitive impairment (MCI), and AD dementia were analyzed using the NULISAseq CNS panel (N =1344; CU N =499). Amyloid positivity (A+) was defined using CSF pTau181/Aβ42 >0.025; PET A+ was defined as Centiloid >24.1. Cross-sectional amyloid classification was evaluated using area under the ROC curve (AUC) with DeLong tests and FDR correction. Exploratory prognostic analyses assessed baseline plasma biomarkers for predicting progression from A- to A+ PET and CU to MCI (or MCI/AD) using time-to-event models.

Results: BD-pTau217 was the top-performing marker in identifying CSF A+ in all participants (AUC =0.91,95%CI 0.90-0.93) and significantly outperformed total pTau217 (ΔAUC =0.023, FDR p=1.3x10-8) and other p-tau markers including BD and total versions of pTau181 and pTau231. Similarly, in CU participants, BD-pTau217 again ranked highest (AUC =0.87,95%CI 0.84-0.91) and remained significantly better than total pTau217 (ΔAUC =0.030, FDR p=0.001). Interestingly, using amyloid PET as the reference standard, discrimination was higher but not significantly different between BD-pTau217 and total pTau217 (AUC =0.94,95%CI 0.92-0.96 vs 0.93,95%CI 0.91-0.95, FDR p=0.06 in full cohort; AUC =0.92,95%CI 0.88-0.96 vs 0.91,95%CI 0.87-0.95, FDR p=0.68 in CU participants). Yet, BD-tau version pTau231 and pTau181 substantially improved these biomarker accuracies compared to total p-tau versions. Exploratory analyses of progression showed similar prognostic performance for BD and total pTau217 for A+ PET and clinical progression, with comparable hazard separation and time-dependent discrimination.

Conclusions: We report one of the first large-scale comparisons of brain-derived versus total plasma pTau217 in ADNI. Brain-derived p-tau biomarkers provide significant value for detecting CSF-defined amyloid pathology and markedly improved performance of pTau231 and pTau181, while pTau217 remains the most accurate plasma marker overall. These findings inform interpretation and potential clinical trial utility of next-generation blood-based tau biomarkers.

POSTER # 24

LONGITUDINAL PROGNOSTIC VALUE OF BRAIN-DERIVED AND TOTAL PLASMA PTAU BIOMARKERS FOR AMYLOID AND CLINICAL PROGRESSION IN ADNI. Ghisays V, Denkinger MN, Singh A, Marques T, Malek-Ahmadi M, Van-Keuren Jensen K, Protas H, Sohankar J, Goradia D, Devadas V, Chen Y, Li S, Langbaum JB, Weiner M, Reiman EM, Su Y, Ashton NJ for The Alzheimer's Disease Neuroimaging Initiative. Banner Alzheimer's Institute; Banner Sun Health Research Institute; Translational Genomics Research Institute; University of California, San Francisco; Arizona Alzheimer's Consortium.

Background: Plasma phosphorylated tau (pTau) biomarkers are increasingly used for Alzheimer's disease (AD) detection, treatment decision-making, and clinical trial enrichment. Recent immunoassay modifications for pTau217 that selectively isolate brain-derived tau 217 (BD-pTau217) have demonstrated improved diagnostic performance. However, the improved longitudinal prognostic value of these new brain derived assays remains unclear.

Methods: Plasma samples from ADNI1/GO/2/3 participants analyzed using the NULISAseq CNS panel (N=1427; cognitively unimpaired [CU] N=529) were studied. Amyloid PET positivity (A+) was defined as Centiloid >24.1. Associations of baseline plasma biomarkers with longitudinal amyloid PET conversion (A− to A+) and clinical progression (CU to MCI/AD) were evaluated using Cox proportional hazards models and time-dependent area under the ROC curve (tdAUC), with paired biomarker comparisons performed in secondary analyses.

Results: Baseline plasma BD-pTau217 demonstrated strong prognostic performance for future amyloid PET progression among evaluated plasma biomarkers. For A− to A+ progression, BD-pTau217 showed higher discrimination than total pTau217 at earlier follow-up intervals, with tdAUCs of 0.82 vs 0.69 at 2.5 years and 0.77 vs 0.64 at 4 years. BD-pTau217 was also associated with substantially higher risk of A− to A+ progression (HR 10.54 [95% CI 2.3-48.1] at 2.5 years; HR 7.03 [1.9-25.6] at 4 years), whereas total pTau217 showed weaker and non-significant associations. In contrast, prognostic performance for clinical progression (CU to MCI/AD) was similar between BD- and total pTau217, with modest and overlapping discrimination (tdAUC ~0.59-0.60 at 2.5-4 years; HRs ~2.6-2.8).

Conclusions: We report one of the first large-scale comparisons of brain-derived versus total plasma pTau217 utilizing ADNI. Plasma pTau217 provided robust prognostic information for both biological and clinical disease progression. Assays selectively targeting brain-derived pTau217, however, showed improved prediction of future amyloid PET progression, consistent with greater specificity for early AD pathology. In contrast, differences between brain-derived and total pTau217 were modest for near-term clinical progression, suggesting that both measures capture similar information at symptomatic stages.

POSTER # 25

CAREPRO LTC: PILOT STUDY RESULTS. Glinka A, Gonzalez-Pyles S, Carll P, Santos S, Jaszewski A, Pohl J, Coon DW. Arizona State University; Arizona Alzheimer's Consortium.

Background: In 2025, approximately 7.2 million Americans were living with Alzheimer's and the incidence is growing every year. As the person needs more assistance, people with Alzheimer's disease and related dementias (ADRD) can be placed in assisted living communities making up to 34% of the residents, with 61% of these residents having moderate or severe cognitive impairment. These proportions are even higher among residents of memory care facilities. Family caregiving and its related stressors and distress do not end with placement and interventions for these caregivers are lacking. CarePRO-LTC adapted the evidence-based caregiver intervention, CarePRO, by focusing on the key stressors and concerns of family caregivers who have placed their loved ones with ADRD in long-term care (LTC) facilities.

Methods: CarePRO-LTC is a 5-week, skills-based intervention that combines weekly 2.5-hour interactive group sessions with weekly 30-minute individual telephone coaching sessions. In this single-arm pilot study, all group sessions were delivered remotely via Zoom. The virtual format was selected to increase access for family caregivers where work obligations, geographic location, transportation limitations, personal health concerns, or limited respite care preclude in person attendance. Care-PRO-LTC emphasizes practical skill development that caregivers can apply to the evolving challenges associated with ADRD in LTC. During group sessions, participants practice new strategies through demonstrations, role-playing activities, and guided discussion, while individual coach sessions reinforced skill use and provide personalized feedback. Study outcomes were assessed through telephone interviews lasting approximately 45 minutes administered at baseline (within two weeks before the first workshop) and after the end of the intervention (within two weeks of the last coaching session).

Results: Twenty-nine family caregivers across 18 states participated in the study (mean age = 67.9 years; 69% female). Post-intervention, caregivers demonstrated significant improvements in emotional well-being, including reductions in depressive symptoms, worry, loneliness, anger, caregiving-related stressors, and negative coping strategies. Significant gains were also observed in caregiving confidence and preparedness, leisure time and social support satisfaction, and positive aspects of caregiving. Effect sizes were moderate to large, with the greatest improvements in caregiving-related stressors, preparedness for caregiving, and caregiving self-efficacy. Participants viewed the intervention favorably, with all caregivers reporting at least some benefit and 93% reporting a great deal of overall benefit.

Conclusions: Results for the pilot trial suggest that CarePRO-LTC is a promising, virtually delivered intervention for family caregivers of individuals with ADRD residing in long-term care. The virtual format has the potential to expand access for caregivers who face barriers to participating in in-person programs. These findings support continued refinement of CarePRO-LTC and its evaluation through a larger RCT.

POSTER # 26

DESIGNING AN AI CHATBOT FOR OLDER ADULTS WITH COGNITIVE DECLINE LIVING ALONE: A QUALITATIVE STUDY OF USER NEEDS AND DESIGN PRIORITIES. Gómez-Morales A, Bahrami R, Turaga P. Arizona State University; Arizona Alzheimer's Consortium.

Background: Artificial intelligence (AI)-based chatbots have the potential to support older adults experiencing age-related cognitive changes by providing personalized assistance with daily activities, health management, and social engagement. However, the successful development of AI technologies requires an understanding of end-user needs, preferences, and priorities. This study explored older adults' perspectives regarding the desired functions and design characteristics of an AI chatbot for aging in place, cognitive health, and everyday functioning.

Methods: To date, three focus groups were conducted with community-dwelling older adults (N=13). Conversations explored participants' experiences with ADRD/MCI-related cognitive changes and their perceptions of how an AI chatbot could support daily functioning, cognitive health, safety, and well-being. Focus groups held via Zoom were audio-recorded, transcribed verbatim, and analyzed using thematic analysis. NVivo and Excel were used to support data organization, coding, theme development, and figure creation.

Results: Four overarching themes were identified and translated into nine user-centered design priorities for AI chatbot development: "supporting everyday independence and organization," "promoting cognitive health and decision support," "enhancing safety while preserving independence," and "fostering social connection through accessible and personalized interaction." Participants emphasized medication management, routine reminders, cognitive stimulation activities, evidence-based health information, safety monitoring, companionship, voice-based communication, and personalized support. These findings informed nine preliminary design priorities: safety and risk mitigation; medication management; routine scaffolding; adaptive accessibility; navigation and mobility support; task sequencing and executive planning; instrumental activities of daily living; social companionship; and cognitive maintenance.

Conclusions: Older adults envisioned an AI chatbot that extends beyond information delivery to provide integrated support for daily living, cognitive health, safety, and social engagement. Findings highlight the importance of user-centered design to ensure the product developed aligns with users' needs and goals, an approach that prioritizes accessibility, personalization, and trustworthiness when developing AI technologies intended to support vulnerable aging populations. These findings provide foundational guidance for the development of user-centered AI chatbot interventions designed to support aging in place, maintain independence, and enhance quality of life among older adults experiencing cognitive changes.

POSTER # 27

RESOLUTION HARMONIZATION OF PET IMAGING USING DEEP 3D CONVOLUTIONAL NEURAL NETWORKS. Goradia DD, Luo J, Devadas V, Solankar J, Li S, Wu T, Li B, Reiman EM, Su Y. Banner Alzheimer's Institute; Arizona State University; University of Illinois - Chicago; Arizona Alzheimer's Consortium.

Background: Variability in PET image resolution arising from differences in scanner characteristics and reconstruction algorithm limits cross-study comparability and affects downstream quantitative analysis. We propose a deep learning–based PET resolution harmonization framework that is agnostic to native scanner resolution and does not require prior knowledge of scanner or reconstruction parameters. A deep 3D convolutional neural network (3DCNN) is used to directly predict standardized 6 mm and 8 mm full width at half maximum (FWHM) PET images from native scanner-resolution inputs. Harmonization performance is evaluated using SPM12-derived mean cortical standardized uptake value ratios (MCSUVR) and amyloid-β positivity classification to assess quantitative and clinical agreement between predicted and reference scans.

Methods: A total of 2,833 paired 3D PET scans from the Alzheimer's Disease Neuroimaging Initiative (ADNI), including native scanner-resolution images and corresponding 6 mm and 8 mm FWHM smoothed images, were split into training (n=1,700), evaluation (n=567), and independent testing (n=566) sets. A fully convolutional deep 3DCNN consisting of six 3D convolutional layers with batch normalization and ReLU activations was trained to learn voxel-wise resolution transformations from native scanner resolution to 6 mm and 8 mm targets. The network preserves image matrix size and performs filtering without explicit downsampling or upsampling. Models were trained using voxel-wise mean squared error loss optimized with Adam (learning rate=5×10^{-4}) for 50 epochs. Predicted and reference images were processed using SPM12 for spatial normalization and MCSUVR computation, and amyloid-β positivity was assessed using an MCSUVR threshold of 1.17.

Results: Predictions from native scanner resolution to 6 mm demonstrated strong quantitative agreement with reference images, with high MCSUVR correlation ($r=0.99$, $p<0.001$) and high classification concordance (sensitivity=1.000, specificity=0.983, balanced accuracy=0.992, Cohen's $\kappa=0.977$). Native scanner resolution to 8 mm predictions yielded similarly high MCSUVR correlation ($r=0.99$, $p<0.001$) and near-perfect classification agreement (sensitivity=1.000, specificity=0.997, balanced accuracy=0.999, Cohen's $\kappa=0.996$).

Conclusions: This scanner-agnostic, fully convolutional deep 3DCNN framework enables robust harmonization of native scanner-resolution PET images to standardized 6 mm and 8 mm resolutions while preserving MCSUVR and amyloid-β positivity classification. The approach supports resolution-consistent, scanner-independent PET analysis and improved cross-study comparability.

POSTER # 28

TIME-RESTRICTED EATING IN ALZHEIMER'S DISEASE: THE TREAD TRIAL. Gunning JA, Hettiwatte Y, Zaniletti I, Smith T, Aliskevich E, Khan N, Eagan D, Krell-Roesch J, Geda YE, Racette SB. Arizona State University; Barrow Neurological Institute; IZ Statistics LLC; Karlsruhe Institute of Technology; Arizona Alzheimer's Consortium.

Background: Time Restricted Eating (TRE) is a form of intermittent fasting that is characterized by a restricted eating window and extended fasting periods. TRE may favorably affect cognition via several potential mechanisms. Prolonged fasting periods result in ketone production and metabolic switching from glucose to fatty acid and ketone utilization, leading to a cascade of adaptive metabolic and cellular responses. In Alzheimer's Disease (AD), glucose uptake is impaired; however, ketones remain a viable energy source. The objectives of the TREAD study are 1) to determine the feasibility of a TRE intervention among individuals with MCI and 2) to assess the impact of TRE on cognitive function and biomarkers of metabolic health and AD.

Methods: TREAD is a pilot trial of a 12-week TRE intervention in individuals with MCI characterized by a 16-hour fast and an 8-hour eating window on five or more days/week. Eligible participants are aged 55-89 years with a supportive study partner to encourage adherence to the intervention. Participants are asked to record their first and last caloric intake each day in a phone-based app. Feasibility measures include participant enrollment, retention, adherence to the intervention, and study completion. Cognitive function measures include MMSE, CTMT, WAIS-IV, Digit Span subtest, category and phonemic fluency, and the AVLT. Blood biomarkers of AD are measured by Quanterix Laboratory (Simoa) and include amyloid beta (Aβ) 42/40, phosphorylated (p)-tau 217, p-tau 181, and total (T)-tau. Blood biomarkers of metabolic health include hemoglobin A1c (HbA1c), fasting glucose and insulin, high sensitivity C-reactive protein (hsCRP), and inflammatory biomarkers.

Results: To date, 31 participants have been enrolled and 28 participants have completed the study. Baseline characteristics, reported as mean (SEM), are: 64.2% male, age 72.3 (1.1, range 63-82) years, BMI 27.4 (0.9) kg/m2, MMSE score 25.4 (0.6), Trail Making A score 70.2 (6.9) seconds, Trail Making B score 112.7 (9.5) seconds, Aβ42/40 0.033 (0.002), p-Tau 217 0.16 (0.12) pg/mL, p-Tau 181 48.63 (8.01) pg/mL, and T-tau 3.08 (0.26) pg/mL, HbA1c 5.5 (0.10)%, fasting glucose 92.9 (3.2) mg/dL, fasting insulin 3.8 (0.52) μIU/mL, and hsCRP 1.63 (0.35) mg/L. Feasibility and adherence to the TRE intervention were high; the mean eating window among participants was 7.58 hours. Participants were within an 8-hour window on 78.2% of all days, indicating that they followed the TRE protocol on at least five days each week. Exit survey data indicate that 95% of participants who completed the intervention are likely to follow TRE long term, further demonstrating that TRE is feasible in older adults with MCI.

Conclusions: Overall, these preliminary data indicate that TRE is highly feasible, well-accepted, and safe in older adults with MCI. Completion of the remaining participants and further analyses will reveal the potential impact of TRE on cognition and blood biomarkers in individuals with MCI.

POSTER # 29

CHRONIC CORTICOSTERONE EXPOSURE INDUCES PHENOTYPIC CHANGES IN MURINE ASTROCYTES: IMPLICATIONS FOR STRESS-ASSOCIATED METABOLIC DYSFUNCTION IN ALZHEIMER'S DISEASE. Gusek B, Mody A, Lawson K, Bussey K. Midwestern University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) involves cognitive decline, amyloid-beta plaques, and neurofibrillary tangles. Chronic stress and metabolic dysfunction are environmental contributors to AD risk. Impaired cerebral glucose metabolism is an early AD feature. Glucocorticoids, elevated during chronic stress, oppose insulin signaling and disrupt glucose homeostasis. Astrocytes are critical regulators of brain energy metabolism; however, how prolonged glucocorticoid exposure alters their phenotype remains poorly understood.

Methods: Murine C8-D1A astrocytes were cultured under three conditions over 28 days: control, corticosterone-selected (1 μM, 28 days), and reverted (corticosterone for 14 days followed by 14 days in normal media). HoloMonitor live-cell imaging was conducted over 48 hours with frames every 30 minutes. Morphology was assessed at 30 minutes and 25 hours, quantifying cell area, irregularity, average optical thickness, and shape convexity. Proliferation, migration, and motility were continuously monitored. Imaging data were analyzed by one-way ANOVA with Tukey's post-hoc test. Lysates from days 0, 6, 12, and 18 were analyzed by immunoblotting for glucocorticoid receptor (GR), phospho-GR (S211), and the glucocorticoid-inducible protein FKBP5.

Results: Corticosterone-selected and reverted cells showed reductions in cell area compared to controls at both time points ($p<0.0001$). Cell irregularity was reduced in selected and reverted cells at 30 minutes ($p<0.0001$), persisting at 25 hours ($p=0.0347$). Average optical thickness was also reduced in selected cells at both timepoints ($p<0.0001$). Shape convexity was significantly altered across all groups at both timepoints ($p<0.05$). Reverted cells showed markedly elevated proliferation compared to controls and selected cells, while selected cells exhibited reduced migration and motility. Immunoblotting revealed total GR was stable across all conditions, and FKBP5 expression increased in selected cells but returned to baseline by day 12 in reverted cells.

Conclusions: Both selected and reverted cells displayed sustained morphological remodeling in murine astrocytes, reducing cell size, complexity, intracellular density, and migratory capacity. Importantly, these changes persisted even after FKBP5 returned to baseline, suggesting persistent gene expression alterations that do not require continued glucocorticoid signaling. These findings support a cellular mechanism linking chronic stress to AD vulnerability.

POSTER # 30

THE IDENTIFICATION OF FLUID BIOMARKERS ASSOCIATED WITH COGNITIVE DECLINE IN SPORADIC PARKINSON'S DISEASES. Hanley D, Denkinger MN, Ghisays V, Marques TM, Brazel D, Quereshi F, Singh A, Dieckhoff K, Brumm M, Coffey C, Hutten SJ, Frasier M, Marek K, Simuni T, Merchant K, Jensen K, Ashton NJ for Parkinson's Progression Markers Initiative (PPMI). Banner Alzheimer's Institute; Banner Sun Health Research Institute; The Michael J. Fox Foundation for Parkinson's Research; Parkinson's Progression Markers Initiative; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Parkinson's Disease is the second most common neurodegenerative disorder worldwide. Approximately 25–30% of individuals diagnosed with sporadic Parkinson's disease (sPD) develop cognitive impairment within 10 years of diagnosis, representing a major determinant of disease burden and progression. Early clinical diagnosis remains challenging, with reported misdiagnosis rates approaching 30% during the first two years following symptom onset. Importantly, motor symptom severity does not reliably predict subsequent cognitive decline, limiting the ability to identify patients at risk of progression to Parkinson's disease dementia. Biomarker-based approaches capable of detecting early molecular changes associated with neurodegeneration and cognitive decline may provide a valuable strategy for identifying high-risk patients prior to clinical deterioration.

Methods: A total of 235 participants with clinically diagnosed PD were included from the Parkinson's Progression Markers Initiative (mean [SD] age: 61.6 [9.4] years; 78 females, 30.2%). During 4 years of follow-up, 54 participants (mean [SD] age: 65.7 [8.2] years; 14 females, 38.5%) developed cognitive impairment, while 181 participants (mean [SD] age: 60.4 [9.4] years; 65 females, 27.8%) remained cognitively stable. Cerebrospinal fluid (CSF) samples collected at baseline and final follow-up visits were analyzed using the NULISAseq CNS and Inflammation panels. Differential protein expression analyses were performed in R, with correction for multiple testing.

Results: Individuals who subsequently developed cognitive impairment demonstrated significantly higher baseline concentrations of several phosphorylated tau species, including brain-derived and total p-tau231, p-tau217, and p-tau181, suggesting early tau-related neurodegenerative processes preceding clinical cognitive decline. Baseline concentrations of neurofilament light chain (NfL), a marker of axonal injury, were also significantly elevated in individuals who progressed. In addition, nominal differences were observed in several immune- and glial-associated markers, including TREM1, CD80, IL2RB, IL7R and CXCL9, indicating a differential neuroimmune activation and glial dysfunction in patients at increased risk of cognitive decline.

Conclusions: These findings demonstrate that molecular changes associated with tau pathology, axonal injury, and neuroimmune dysregulation are detectable in CSF prior to the onset of cognitive impairment in sporadic PD. The identification of biomarker signatures associated with future cognitive decline may enable earlier risk stratification, improve patient selection for clinical trials, and provide new insights into the biological mechanisms underlying progression to Parkinson's disease dementia. Longitudinal biomarker profiling may represent a critical step toward precision medicine approaches in PD.

POSTER # 31

ENROLLING OLDER ADULTS INTO AN ADRD RESEARCH REGISTRY VIA ELECTRONIC HEALTH RECORD MESSAGE: A FEASIBILITY STUDY. Harkins K, Bleakley A, Maloney E, Adams M, Langbaum, JB. University of Pennsylvania; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Addressing the public health challenge of Alzheimer's Disease and Related Dementias (ADRD) requires studies to enroll a large number of participants who are representative of individuals with ADRD or those at high-risk for developing the disease. There is growing interest in Electronic Health Record (EHR) patient portals as research recruitment tools, but evidence of their effectiveness is needed. Previous research has developed theory-driven, evidence-based messages to recruit cognitively healthy older adults into ADRD research registries via social media ads. This pilot study assessed the feasibility of deploying these messages through the EHR.

Methods: We identified Penn Medicine patients who met the following criteria: (1) age 50 to 80 (2) "activated" EHR patient portal, (3) residing in zip codes indicating proximity to Penn campus (4) no diagnoses indicating cognitive impairment, and (5) opted-in to EHR contact for research. We targeted an equal split among invites sent across the following demographic characteristics: race and ethnicity (non-Latino White, Black, and Hispanic/Latino), age (50-59, 60-69, and 70-80), and sex (female and male). Messages invited patients to join the Penn Memory Center Brain Health Research Registry.

Patients who received the message could select "not interested" or "interested." Those who responded "interested" received a follow-up message with a link to join the registry, which requires providing contact and demographic information. We tracked rates of joining the registry overall and within demographic groups.

Results: During the 4-week recruitment period, 693 recruitment messages were sent. The response rate was 27.0% and 75 patients enrolled for a join rate of 10.5%. Join rates were similar for men and women (11.3% and 10.1%, respectively) and across age groups (50-59: 9.6%, 60-69: 10.8%, 70-80: 12.3%) (all $\chi 2 > 0.05$). Differences were seen between racial and ethnic groups, with the highest join rate for non-Latino White patients (16.2%) followed by Hispanic patients (8.9%) and Black patients (7.7%) ($\chi 2 = 0.006$).

Conclusions: Conclusion: Evidence-based recruitment messages developed for social media were an efficient means of enrolling older adults into an ADRD research registry through the EHR. EHR outreach may be more effective at enrolling non-White participants and men than social media ads at lower cost.

POSTER # 32

MAKING MEANING, SHARING STORIES: REFRAMING THE SEMANTIC SHIFT IN AUTOBIOGRAPHICAL MEMORY. Hennessy S, Andrews-Hanna J, Grilli, M. University of Arizona; Arizona Alzheimer's Consortium.

Background: Aging is associated with changes in autobiographical recall; compared to younger adults, older adults recall fewer specific, episodic details and more semantic and 'gist'-like details. While some attribute this shift to age-related cognitive decline, others suggest it may reflect an adaptive change in narrative style. Semantic details may serve to situate events within an individual's broader life story ("time integration") or to highlight their personal significance ("meaning integration"), potentially reinforcing self-continuity or enhancing communication or social connection. However, how aging relates to these forms of autobiographical integration, and their links to semantic details, and self and social functions, remain underexplored.

Methods: This project investigated the self and social functions of autobiographical memory integration in two pre-registered studies. In Study 1, we explored age-related differences in meaning and time integration, testing whether personal semantic details drive these integrative tendencies and if they predict self-continuity (N = 157 older adults aged 60+; N = 44 younger adults aged 18-30). In Study 2, we investigated whether increased autobiographical integration, as observed in older adults, may confer social or communication benefits. We experimentally manipulated time and meaning integration in synthetic memories and assessed whether a separate, representative online cohort of adults (N = 300, aged 18-82) perceive integrated memories (time and/or meaning) as more clear, authentic, informational, relatable, interesting, or vivid than non-integrated memories.

Results: In Study 1, older adults showed greater meaning, but not time, integration than younger adults, and personal semantic details predicted both forms, though integration was not associated with self-continuity. In Study 2, at least one form of integration raised recipient ratings of all outcomes above those for fully non-integrated memories, with either form alone sufficient for most outcomes, and informativeness benefiting from both.

Conclusions: Together, these findings suggest that the semantic shift in aging may reflect meaning integration, which may serve adaptive communicative benefits rather than pure decline, opening new avenues for understanding the functions of non-episodic details in autobiographical memory.

POSTER # 33

LONGITUDINAL AND PREDICTIVE MODELING OF CSF PROTEOMICS IN PSEN1 E280A MUTATION CARRIERS. Henscheid N, Denkinger MN, Ghisays V, Karten YJ, Klein G, Brown C, Stephenson D, Bittner T, Alexander RC, Romero K, Tariot PN, Reiman EM, Langbaum JB, Ashton NJ. Critical Path Institute; Banner Alzheimer's Institute; Hoffmann-La Roche Ltd; Arizona Alzheimer's Consortium.

Background: Autosomal dominant Alzheimer disease (ADAD) caused by the PSEN1 E280A mutation follows a predictable clinical course, enabling biomarker trajectories to be evaluated relative to the expected time of symptom onset. The Alzheimer's Prevention Initiative (API) ADAD Colombia Trial (NCT01998841) enrolled cognitively unimpaired mutation carriers and non-carrier relatives, with carriers randomized to crenezumab or placebo for five years. Although crenezumab did not significantly slow cognitive decline, the study included a rich set of imaging and fluid biomarkers and cognitive assessments over multiple timepoints. The current study uses longitudinal cerebrospinal fluid (CSF), imaging, and cognitive data outcomes to characterize proteomic changes relevant to future prevention trials in ADAD and potentially sporadic Alzheimer disease.

Methods: Cerebrospinal fluid (CSF) samples from individuals who had all three longitudinal time points available—18 non-carriers, 28 placebo-treated carriers, and 29 crenezumab-treated carriers—were analyzed using the Alamar NULISAseq CNS disease panel. Longitudinal mixed effects models were used to evaluate protein trajectories by carrier status, treatment arm, time, and estimated years from expected symptom onset. Protein changes were related to amyloid PET, tau PET, MRI atrophy, and cognitive trajectories. Pathway enrichment, co-expression modules, principal component analysis, regularized regression, and cross validated machine learning models were used to prioritize biologically coherent and parsimonious signatures.

Results: Analyses focused on identifying CSF proteins with longitudinal trajectories that differed by PSEN1 E280A carrier status and proximity to expected symptom onset. Candidate proteins showing distinct temporal patterns across groups provided an initial assessment of whether treatment exposure modifies selected proteomic trajectories. Proteomic features and protein modules were evaluated for associations with amyloid PET, tau PET, MRI atrophy, and cognitive change. Parsimonious multianalyte signatures were explored for improved carrier classification, prognostic modeling, and evaluation of trial enrichment strategies beyond standard clinical and demographic covariates.

Conclusions: Longitudinal CSF NULISAseq profiling in the Colombia API cohort may provide a staged map of proteomic change across PSEN1 E280A ADAD. Prioritized proteins and multianalyte signatures may support biologic staging, participant stratification, endpoint selection, and prognostic adjustment in future prevention trials, with planned evaluation in sporadic AD and Down syndrome cohorts.

POSTER # 34

THE ALZHEIMER'S PREVENTION REGISTRY AND GENEMATCH PROGRAM: A WEB-BASED MODEL FOR PUBLIC ENGAGEMENT, AWARENESS, AND PARTICIPANT RECRUITMENT IN ALZHEIMER'S-RELATED RESEARCH. High N, Ochoa C, Salata H, Gordon D, Langbaum JB. Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: The Alzheimer's Prevention Registry (APR) and its GeneMatch program serve as web-based recruitment platforms designed to enhance public awareness, foster interest, and facilitate participation in Alzheimer's-related research studies. The programs complement and supplement researchers' local recruiting efforts by connecting them with potential study participants. To accomplish this, concerted efforts are required to continually enroll registry members reflective of the general population, maintain their engagement in the program and interest in research participation, and offer a range of study opportunities.

Methods: Adults age 18 and older are eligible to join APR at www.endALZnow.org. At registration, individuals provide contact and demographic information and are prompted to subscribe to relevant email lists. The APR team works with researchers to promote Alzheimer's-related studies to members. APR members receive email communication for engagement purposes and are notified when new study opportunities are available. Members interested in a study fill out an online contact form with their name, email address and phone number, review and acknowledge the study's eligibility criteria and authorize APR to share their contact information with the enrolling study team. The APR team provides enrolling studies with a secure dashboard for tracking referrals. Concerted efforts have focused on research to understand motivators and facilitators of joining a registry and developing evidence-based communication messages to increase registry participation. GeneMatch, while not currently enrolling new participants, includes US-based adults ages 50-90 who self-report not having a diagnosis of cognitive impairment. After consenting to GeneMatch, participants are sent a buccal self-swab kit to complete and return to the CAP/CLIA-accredited lab for DNA extraction and APOE genotyping. GeneMatch does not return the APOE results to participants.

Results: Since launching in May 2012, more than 389,000 individuals have joined APR (mean age 69; 76 percent female; 93 percent cognitively unimpaired). APR has supported recruitment for 204 studies nationwide, 30 of which were Arizona-based studies. APR currently assists 32 studies, including 14 Arizona-based studies. Email newsletters show strong engagement with 34 percent open rates and 10 percent click rates. Since late-2019, more than 14,500 members expressed interest in a study, including more than 4,600 Arizona-based study referrals. GeneMatch has enrolled 117,693 participants since November 2015 and has supported 30 studies.

Conclusions: Online registries can be effective solutions to efficiently connect volunteers to studies. Future work explores improving user experience and understanding how engagement strategies influence study participation.

POSTER # 35

DISSOCIATED MAS1 RECEPTOR AND EFFECTOR EXPRESSION IDENTIFIES A FAILED COMPENSATORY STATE IN HUMAN VASCULAR COGNITIVE IMPAIRMENT: IMPLICATIONS FOR THERAPEUTIC STRATEGY. Hoyer-Kimura C, Huentelman M, Hay M. University of Arizona College of Medicine - Tucson; Sarver Heart Center; Evelyn F. McKnight Brain Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Vascular contributions to cognitive impairment and dementia (VCID) are increasingly understood as disorders of distributed neurovascular unit (NVU) dysfunction involving endothelial injury, chronic inflammation, oxidative stress, and impaired neurovascular coupling. Despite the major contribution of vascular pathology to dementia, the transcriptional architecture of human VCID brain tissue and the status of endogenous vasoprotective signaling pathways remain incompletely characterized. We investigated whether coordinated pathway-level dysregulation in human VCID tissue reveals evidence of endogenous compensatory signaling within the MAS1/ANG-(1-7) vasoprotective axis and whether this architecture may identify mechanistically relevant therapeutic entry points.

Methods: We performed differential gene expression analysis (DESeq2 v1.38.0) and pre-ranked gene set enrichment analysis (fgsea v1.24.0, 1,000 permutations) on bulk RNA-sequencing data from post-mortem superior parietal lobe tissue of 40 individuals (GEO; 19 neuropathologically confirmed VCID, 21 age-matched controls; model: ~PMI + age + sex + condition). A custom a priori 55-gene MAS1/ANG-(1-7) pathway gene set was evaluated alongside MSigDB v2023.1 pathway sets. Specimen-level Spearman correlation analyses assessed relationships between MAS1 receptor expression, NF-κB pathway drivers, downstream vascular effectors, and endothelial activation markers. Single-nucleus RNA-sequencing data (GEO) were interrogated to assess endothelial localization of MAS1-associated signaling genes. PI3K-Akt leading-edge decomposition analyses evaluated inflammatory and vasoprotective signaling architecture.

Results: No individual gene reached FDR

Conclusions: Human VCID brain tissue exhibits coordinated pathway-level dysregulation consistent with chronic NVU stress and inflammatory activation. Simultaneous engagement of downstream MAS1-associated vasoprotective effectors alongside inverse associations between MAS1 receptor expression and inflammatory signaling is consistent with a transcriptionally engaged but receptor-constrained protective program, suggesting a failed compensatory state within the NVU. These findings support further investigation of therapeutic strategies designed to restore upstream MAS1 receptor-level signaling within an already engaged downstream vasoprotective network and reinforce the importance of vascular and endothelial biology as therapeutic targets in VCID.

POSTER # 36

THE MINDCROWD MOBILE LABORATORY: LONGITUDINAL MULTIMODAL PHENOTYPING TO ENGAGE RURAL COMMUNITIES IN COGNITIVE AGING RESEARCH. Huentelman M, Johnson M, Price C, Barraza Y, Chambers D, Metz D, Moore B, Beres S, De Both M, Dumitrascu O, Ryan L. Translational Genomics Research Institute; Mayo Clinic Arizona; University of Arizona; Arizona Alzheimer's Consortium.

Background: Rural residents are underrepresented in cognitive aging research, limiting the generalizability of biomarker discovery, risk prediction, and resilience models. These communities often experience disproportionate burdens of vascular and other modifiable risk factors, as well as structural barriers to specialty care and research participation. We developed the MindCrowd mobile laboratory (MC-mLab) to deliver longitudinal, multimodal brain health research directly to communities across Arizona, with intentional outreach to rural zip codes.

Methods: The MC-mLab is a truck and customized trailer containing dedicated wet laboratory space and a neuroimaging suite, enabling approximately 90-minute research visits in community settings. Participants complete cognitive testing focused on verbal associative memory and processing speed, allowing comparison with the larger MindCrowd online cohort of approximately 900,000 participants. Additional phenotyping includes bilateral grip strength, blood pressure, bioimpedance-based body composition, and 16-item odor identification testing. Ultra-low-field brain MRI is acquired using the 64 mT Hyperfine Swoop platform, including T1, T2, and FLAIR sequences. Retinal fundus imaging is collected using the Optomed Aurora IQ and analyzed with AutoMorph. Capillary blood is processed on-site for genome-wide SNP genotyping, DNA methylation profiling, and plasma proteomics using the Alamar NULISA CNS 120 panel. Participants are invited for annual follow-up.

Results: As of June 2026, the MC-mLab has completed 1,831 baseline visits, 276 one-year follow-up visits, and 114 two-year follow-up visits, averaging approximately 65 visits per month. Recruitment demonstrates strong reach into understudied populations, including rural zip code residents (35%), participants reporting Hispanic ethnicity (19%), lower educational attainment (15% high school diploma or less), and lower socioeconomic status (22% household income ≤$35,000). Cognitive results in the MC-mLab cohort mirror patterns observed in the larger MindCrowd cohort, and APOE allele frequencies are consistent with expectations for a population-based sample. Ultra-low-field MRI measures replicate expected age-associated trends in global brain and hippocampal volumes. Retinal fractal dimension, grip strength, skeletal muscle mass, olfaction, and plasma NfL also demonstrate age-associated findings.

Conclusions: The MC-mLab is a feasible, scalable, field-deployable platform for longitudinal, multimodal cognitive aging research. By integrating portable MRI, retinal imaging, cognitive and frailty phenotypes, genetics, methylation, and plasma biomarkers, this approach can reduce barriers to participation and support discovery of aging trajectories, risk signatures, and resilience factors that better reflect rural and demographically diverse communities.

POSTER # 37

RELATIONSHIPS BETWEEN BRAIN CONNECTIVITY AND LONGITUDINAL MEMORY DECLINE USING NETWORK ANALYSIS AND PARTIAL LEAST SQUARES. Hughes D, Crook S, Braden B. Arizona State University; Arizona Alzheimer's Consortium.

Background: There has been recent evidence to suggest that autistic adults have higher risk of neurodegenerative disease and dementia compared to non-autistic adults. Previous studies have found some age-related brain differences between autistic and non-autistic adults, but how these differences may contribute to increased dementia risk remain unclear. We used a combination of network analysis and partial least squares to identify functional and structural connectivity patterns that correlate with long-term memory decline in both autistic (n=40) and non-autistic (n=33) adults using data from a longitudinal study.

Methods: We obtained T1, diffusion, and functional MRI data. Brain networks with 96 regions of interest were constructed using the CONN and TVB-UKBB pipelines for functional and structural connectivity from participants' first scan. Long-term memory change was measured using the slope of a mixed effects model for the delayed recall (A7) score of the Auditory Verbal Learning Test evaluated 2-5 times across 2-9 years of follow-up. Networks were thresholded and quantified with the Brain Connectivity Toolbox in MATLAB. Network measures were residualized using age and sex as covariates. Behavioral partial least squares was used to identify multivariate correlations between network measures and long-term memory outcomes.

Results: For the non-autistic adults, there was a significant latent variable relationship between structural connectivity and long-term memory change; weaker structural connectivity in classic memory regions (e.g. hippocampus) correlated with greater memory decline. The autistic adults showed significant latent variable relationships between functional connectivity and long-term memory change; weaker, less interconnected, and less organized functional connectivity across the whole brain correlated with greater memory decline. For both cases, there was a significant difference between groups for the latent variable relationship, demonstrating differing relationships between connectivity and memory.

Conclusions: Both the autistic and non-autistic adults showed significant relationships between connectivity and memory decline. We found that, for the non-autistic adults, memory decline was related to structural connectivity patterns that involved classic memory regions (e.g. hippocampus). For the autistic adults, memory decline was related to functional connectivity patterns across the whole brain. These findings suggest the potential for unique MRI based biomarkers to identify increased risk of accelerated memory decline in autistic adults.

POSTER # 38

EXPLORING THE FEASIBILITY AND BENEFITS OF ART THERAPY FOR OLDER ADULTS LIVING IN TEMPORARY SUPPORTIVE HOUSING AND AT RISK FOR COGNITIVE IMPAIRMENT. Hughes TF, de la Montaigne A, Christensen S, Ayala P, Turner T, Parales JV, Mohapatra S. Midwestern University; Arizona College of Osteopathic Medicine; Arizona Alzheimer's Consortium.

Background: Cognitive impairment is prevalent among unhoused older adults. Art therapy has known benefits for older adults with cognitive impairment and for people who are experiencing homelessness. This pilot study aimed to assess feasibility, acceptability, and explore the benefits of an art therapy program in unhoused older adults at risk for cognitive impairment.

Methods: The Opening Minds through Art (OMA) program was implemented at a supportive housing shelter for adults 55 years and older over 8 weekly sessions with individuals who scored between 18 and 26 on the Montreal Cognitive Assessment (MoCA). Feasibility and acceptability were evaluated. A pre-post survey assessed perceived changes in physical, mental, and social health using the PROMIS-16 battery. Individual interviews were conducted to provide a deeper understanding of the participants' experience in the program.

Results: Forty-two clients were interested in participating, among whom 23 met eligibility criteria and 18 enrolled and completed the baseline assessment (mean age 64.5 years; 66.7 percent female; 61.1 percent White; 66.6 percent some college or more; mean MoCA 22.83; mean time unhoused 19.2 months; mean time at shelter 4.74 months). Fifteen participants completed the program (mean attendance 6.3 (range 5-8) sessions), and 14 participants completed the follow-up assessment. Median change in PROMIS domain scores suggests fewer symptoms of depression, anxiety, sleep problems, and pain, and improved social functioning after OMA. Thematic analysis of participant interviews suggest that OMA (1) was a catalyst for personal growth through creative engagement, (2) fostered connection with others, (3) supported overall health and well-being, (4) provided a sense of autonomy and freedom and stress relief, and (5) was a valuable experience to continue and expand. All clients responded that they would participate again and recommend the program to others at the shelter.

Conclusions: A structured, creative, socially interactive intervention in a shelter setting is feasible, acceptable, and beneficial for cognitively vulnerable, unhoused older adults and may be a non-medical way to improve health, wellbeing, and facilitate the transition to stable housing.

POSTER # 39

ANALYSIS OF FUNGAL DNA AND COMPONENTS IN BRAIN TISSUE FROM ALZHEIMER'S DISEASE PATIENTS AND CONTROLS. Jones TB, Chu P, Jentarra G. Midwestern University; Arizona Alzheimer's Consortium.

Background: The presence of microbes in the brain has been suggested to play a role in the development of Alzheimer's disease (AD) pathology. We have previously characterized the presence of bacterial DNA and bacterial components in the brain tissue of AD patients and controls. Likewise, we have also determined how widely nucleic acids from various herpes viruses are present in the brain tissue of these same subjects. In an effort to more completely describe the microbiome of the brain, we have continued this work by using various methods to determine the extent to which fungal organisms may also be present in the brain. Our original intention was to leverage 18S rRNA gene sequencing to broadly characterize the potential presence of fungal DNA in the brain. However, the sequencing lab that was chosen due to their ability to sequence low microbial biomass samples was having difficulty with the method and not immediately accepting samples for analysis. Due to a funding-restricted timeline, we therefore chose other methods that are specific for common fungi or common fungal components, including targeted qPCR and ELISA analyses.

Methods: For qPCR analyses, DNA was extracted from post-mortem superior frontal gyrus (SFG) and medial temporal gyrus (MTG) brain regions of 48 subjects, with 12 subjects per group. Groups included AD patients, patients with mild cognitive impairment (MCI), individuals with significant AD-associated pathology but no cognitive deficits (high pathology controls, HPC), and non-demented normal control (NDN) individuals. For ELISA analyses (Candia albicans antigen and beta-D-glucan), tissue lysates were made from the SFG of 48 subjects, 12 subjects each from the previously listed four subject groups.

Results: To assess whether fungal DNA was present in subject brain tissue, we used qPCR to detect the presence of Candida species DNA. Using this method, we found that ~10% of tissues from both the SFG and MTG were positive for Candida DNA, although differences between subject groups were not statistically significant. To explore the presence of fungal components in SFG brain tissue, we used two ELISA analyses. The first analysis detected antigens from Candida albicans, a common fungal organism in the body. Using that analysis, we found that around 50% of the subjects in each of our four subject groups are positive for Candida antigens in their SFG brain tissue. However, there were no statistically significant differences between subject groups. We then used a second ELISA test to detect beta-D-glucan, a cell wall component present in the majority of fungal organisms. Using this test, we found that varying levels of fungal beta-D-glucan were present in the SFG brain tissue of all 48 tested subjects, with a statistically significant difference between normal and high pathology controls, but not other subject groups.

Conclusions: In conclusion, we have detected Candida species DNA in SFG and MTG brain tissue from a small proportion (~10%) of our subjects. In a larger proportion of our subjects (~50%) we also detected Candida antigens. It is not yet clear if the DNA or antigens represent organisms that have entered or are living in the brain or if these molecules are diffusing into the brain via the bloodstream. The presence of beta-D-glucan in all subjects while Candida antigens and DNA are present in smaller subsets increases the likelihood that other fungal organisms aside from Candida may also be present in the brain or that their molecules may enter the brain and be retained there. As the testing described here was restricted to one common fungal organism and a common fungal cell wall component, the full picture of fungal presence in the brain is largely incomplete and requires additional testing to more fully characterize. We hope to be able to move forward with 18S rRNA gene sequencing analysis in the future, which will provide a more complete picture of fungal presence in brain tissue.

POSTER # 40

A MANGANESE PORPHYRIN COMPOUND HAS SEXUALLY DIMORPHIC EFFECTS ON BRAIN PROTEIN NITRATION IN PARKIN-NULL DROSOPHILA. Juba A, Batinic-Haberle I, Tovmasyan A, Buhlman LM. Midwestern University; Duke University; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Nitric oxide synthase (NOS) is a signaling enzyme regulating neurotransmission, vascular flow and aspects of immunity. Mammals express endothelial, neuronal, and inducible NOS (eNOS, nNOS, iNOS). In conditions of brain inflammation, iNOS expression is triggered to generate peroxynitrite, a reactive oxygen and nitrogen species (RONS), which reacts with protein tyrosine amino acid residues to post translationally modify proteins called nitration. Excess nitration leads to mitochondrial dysfunction and may contribute to neurodegeneration in progressive diseases like Alzheimer's and Parkinson's. nNOS and eNOS are constitutively expressed, activated by calcium, to facilitate synaptic plasticity, maintenance and vasodilation. Drosophila melanogaster has one NOS isoform (dNOS), shown to function like iNOS and nNOS although the function of dNOS in the adult brain is poorly understood. We have previously demonstrated that young parkin-null (park -/-) flies exhibit climbing deficiencies and increased oxidative stress in degenerating dopaminergic neurons of the protocerebral posterior lateral region 1 (PPL1), functionally homologous to the substantia nigra. We have also observed sexually influenced decreases in markers of oxidative stress in non-degenerating brain regions. In the current study, we measured nitration and dNOS expression in the central brain of aged parkin-null flies to determine whether oxidative stress markers increase with age. We raised park -/- flies on MnTE-2-PyP5+ (MnE) a manganese porphyrin that has been shown to convert superoxide free radicals into oxygen and hydrogen peroxide to protect cells from oxidative damage. Therefore, we hypothesized that exposure to MnE would reduce brain protein nitration.

Methods: At eclosion, park +/+ and park -/- flies expressing NOSGAL4-driven GFP were placed on standard or supplemented food with 2 μM MnTE-2-PyP5+. On days 17-20, flies were separated by sex, brains were dissected in 1XPBS, fixed with 3.7% formaldehyde followed by 3 washes with 0.3% PBT, and blocked with 10% NGS in 1XPBT then incubated with a nitro-tyrosine antibody. The next day brains were washed and blocked with NGS, then incubated with a secondary 594 antibody, washed and mounted with Prolong™ diamond then cured overnight. Z-stacks were captured using uniform acquisition parameters with a Leica Confocal. Emission volumes were collected in the central brain using Image-Pro® and divided by the central brain volume. To control for variability between experiments, each ratio was divided by the average value of control female brains.

Results: dNOS levels were decreased in aged park -/- flies yet unaffected by MnE. Brain nitration levels were unaffected by sex or the parkin mutation; however, MnE increased control male nitration, and treated parkin-null females had increased brain nitration compared to treated parkin-null males.

Conclusions: Previous work showed decreased central brain nitration levels in young park -/-flies with increased nitration in males. Here we report no effect of sex or parkin mutation in the central brain of aged flies. dNOS levels are unaffected by sex or the parkin mutation in young flies, here we report decreased levels in park -/- flies. We suspect that dNOS may function more like nNOS in the adult brain, since changes in dNOS levels do not reflect changes in nitration. While MnE did not affect nitration in parkin-null flies, treated females had higher nitration levels than treated males. MnE activity is dependent upon the cellular redox environment; thus, changes in nitration could indicate regulation to a more favorable oxidative state. Preliminary data suggest that sexual dimorphic effects of MnE may be an important piece of information when determining future experimental strategies based on sex.

POSTER # 41

LIGAND-DEPENDENT FPR2 SIGNALING MODULATES MICROGLIAL RESPONSES TO AMYLOID BETA: IMPLICATIONS FOR ALZHEIMER'S DISEASE. Kim H, Sharma P, Getting SJ, McArthur S, Wickstead ES. Icahn School of Medicine at Mount Sinai; Midwestern University; University of Westminster; University of London; Arizona Alzheimer's Consortium.

Background**:** Neuroinflammation is a key feature of Alzheimer's disease (AD), yet anti-inflammatory therapies have shown limited clinical success, highlighting the need to better understand endogenous pathways that promote inflammation resolution. Formyl peptide receptor 2 (FPR2) mediates pro-resolving signaling through ligands such as Annexin A1 (ANXA1) and also interacts with amyloid beta (Aβ), suggesting a potential role in integrating competing inflammatory and resolution signals in AD.

Methods**:** Microglial responses to oligomeric Aβ were investigated in BV2 cells. Briefly, oxidative stress, metabolic activity, NADPH oxidase (NOX) signaling, and resolution-associated phenotypic makers were assessed following Aβ exposure and pharmacological activation of FPR2. To evaluate the relevance of these pathways in human disease, transcriptomic analyses were performed using the AGORA platform. Differential gene expression data from the ROSMAP, MSBB, and MAYO cohorts were examined across AD-vulnerable brain regions, focusing on FPR2, ANXA1, and NADPH oxidase-associated pathways.

Results**:** Exposure of BV2 microglia to oligomeric Aβ induced pronounced metabolic and NOX-dependent oxidative stress in the absence of robust classical inflammatory activation, consistent with a non-canonical microglial activation state. Pharmacological activation of FPR2 attenuated oxidative stress and promoted expression of pro-resolving phenotypic markers, indicating that FPR2 signaling can counteract Aβ-associated microglial dysfunction. Analysis of human post-mortem transcriptomic datasets revealed increased expression of *FPR2*, *ANXA1*, and multiple NADPH oxidase subunits in AD-vulnerable brain regions, suggesting concurrent activation of oxidative stress and endogenous resolution-associated pathways during disease progression.

Conclusion**:** These findings identify FPR2 as a regulator of microglial responses to Aβ and support a model in which FPR2 signaling modulates the balance between oxidative stress and inflammation resolution in AD. Targeting the ANXA1-FPR2 axis may represent a promising strategy to promote endogenous resolution mechanisms and mitigate microglial dysfunction in Alzheimer's disease.

POSTER # 42

THERAPEUTIC OR PROPHYLACTIC TREATMENT WITH PROGRANULIN DIFFERENTIALLY IMPACTS THE INFLAMMATORY RESPONSE. Knudson K, Yang A, Harrison AM, Uppalapati CK, Leyva KJ, Hull EE. Midwestern University; Arizona Alzheimer's Consortium.

Background: Progranulin (PGRN) is a pleotropic signaling molecule whose ultimate biological activity depends on proteolytic processing to granulin (GRN) units at several sites by multiple proteases. Both healthy lysosomes and PGRN levels have been shown to be neuroprotective, reducing the risk of cognitive decline in centenarians who do not suffer from dementia. In addition, a common pathologic feature in neurodegenerative disease (NDD) is lysosomal dysfunction and neuroinflammation. Mutations in the PGRN trafficking receptor Sortilin (SORT1), which leads to altered PGRN localization, are linked to the development of Alzheimer disease (AD). PGRN alters both lysosomal function and the inflammatory response following proteolytic processing to active granulin units. Mutations in GRN (gene encoding PGRN) lead to lysosomal dysfunction and neuroinflammation in frontotemporal dementia (FTD-PGRN) while a brain penetrant PGRN restores lysosomal function to relieve neuronal inflammation and reduce disease pathology.

Methods: Interferon-gamma (IFN-γ) and a mixture of anti-inflammatory cytokines (IL-4, IL-10, TGF-β1 and TGF-β2) were used to polarize microglia to an M1 or M2 phenotype, respectively. Lysosomal function was disrupted with treatment by either hydroxychloroquine or leupeptin. Response to PGRN treatment was assessed by production of IL-1β and IL-6 using qPCR or flow cytometry. Experiments were performed using the HMC3 human microglia and rodent primary microglia. To mimic the disease state, GRN knock-out and GRN knock-down HMC3 cells were used.

Results: PGRN used prophylactically may exacerbate inflammation while PGRN treatment, after the initiation of pathology, appears to reduce the inflammatory response. In addition, results suggest a causal relationship between PGRN, lysosomal function and inflammation. Using a microglial cell line, alkalization of lysosomes induces an inflammatory response and, conversely, treatment with inflammatory cytokines yields alkalized lysosomes. PGRN treatment promotes pro-inflammatory cytokine production, which is potentiated in the disease model of microglial lines with reduced PGRN expression. In addition, dysfunctional lysosomes are associated with increased complosome assembly, altered PGRN production and processing, pathologic shifts in lipid metabolism, and altered RNA processing.

Conclusions: The pro-inflammatory effects of exogenous PGRN on microglia documented here are contrary to the neuroprotective effects described in other contexts. Thus, the activity of PGRN is context dependent. Harnessing the therapeutic potential of neuroprotective PGRN may require the development of an appropriately processed PGRN product to restore lysosomal function and dampen the neuroinflammation associated with a variety of NDD, including FTLD and AD.

POSTER # 43

PREVALENCE OF PTAU-217 POSITIVITY IN COGNITIVELY UNIMPAIRED OLDER ADULTS.
Lal Z, Malek-Ahmadi M, Denkinger MN, Kuramoto A, Shaikh F, Martinez L, DePorte C, Singh A, Marques TM, Atri A, Ashton NJ. Banner Sun Health Research Institute; Banner Alzheimer's Institute; University of Arizona College of Medicine – Phoenix; Arizona Alzheimer's Consortium.

Background: Phosphorylated tau-217 (ptau-217) is an accurate blood-based biomarker that can detect early Alzheimer's disease (AD) pathology and is being implemented in clinical settings identify early AD. Recent studies have shown that ptau-217 can accurately identify amyloid-positive status in cognitively unimpaired (CU) which highlights its future role as a screening tool for individuals who are asymptomatic. The prevalence of ptau-217 positive status in older adults is not established, but is needed in order to establish base rates that will be used in clinical settings.

Methods: Data from 428 cognitively unimpaired older adults from the Longevity Study were used for this analysis. All subjects had a MoCA score of 24-30 or a CDR Global Score of 0. The Roche Elecsys and NULISA Argo Ptau-217 assays were used with ≥0.189 and ≥0.325 cutoffs were applied to Roche assay values. Logistic regression was used to assess the association between ptau-217 positive status and APOE e4 carrier status. Frequencies of ptau-217 positivity were reported for each cutoff value as well as frequencies for Low (<0.189), Intermediate (0.190-0.324), and High (≥0.325) classifications.

Results: The mean age of the sample was 78.09±8.47 (50-102) years with a mean education level of 15.94±1.27 years. Females comprised 70% (n=320) of the sample while 20% of the sample (n=68) were APOE e4 carriers. 64% of the sample had ptau-217 values above the ≥0.189 cutoff and 30% were above the ≥0.325 cutoff. There was an even distribution of individuals in the Low (n=148), Intermediate (n=151), and High (n=129) ptau-217 classifications. Ptau-positive status (≥0.325) was significantly associated with APOE e4 carrier status [OR=2.74 (1.59, 4.71)].

Conclusions: As anti-amyloid treatments move ahead towards secondary prevention strategies, we observed a high prevalence of ptau-217 positivity in CU older adults indicating that amyloid pathology may occur more frequently in older adults, particularly between the ages of 75 and 85. A broader investigation of potential protective factors is needed to determine how individuals at advanced ages with high ptau-217 levels remain CU.

POSTER # 44

EDROP-AD: EVALUATING SELF-SAMPLING FINGER PRICK BLOOD COLLECTION FOR ALZHEIMER'S DISEASE BIOMARKER DETECTION. Langlois C, Enos J, Atri T, Denkinger MN, Erickson C, Walsh T, High N, De Santiago D, Salata H, Ochoa C, Brown C, Dieckhoff K, Liu J, Marques T, Reiman EM, Ashton NJ, Langbaum JB. Banner Alzheimer's Institute; Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Blood biomarkers are emerging as critical tools in the identification of appropriate Alzheimer's disease (AD) research participants as well as in diagnosis and management of neurodegenerative diseases, particularly AD. While blood tests offer a less costly and invasive alternative to traditional methods (e.g., lumbar puncture, brain imaging), measuring biomarkers through venous draws can be logistically challenging, especially in rural or resource-limited areas. The eDROP-AD study evaluated usability, tolerability, and acceptability of self-sampling finger prick blood card collection for measuring plasma p-tau217 and compares result accuracy to venous blood draws, addressing accessibility and scalability challenges in AD biomarker testing.

Methods: The eDROP-AD study is an ancillary study to the Draw-10 study. Draw-10 is an observational study that explored fluctuations in blood biomarkers over a short period and potential associated drivers. Draw-10 enrolled 100 participants from the Phoenix and Tucson areas, aged 50 – 80 with normal cognition or MCI (screening MoCA of ≥18). Over 9 weeks, participants provided 10 fasting venous blood samples and completed questionnaires assessing alcohol use, exercise, stress and sleep quality. Draw-10 participants in the Phoenix area were invited to participate in eDROP-AD. Enrolled participants completed self-sampling at Banner Alzheimer's Institute using 2 Capitainer SEP10 cards. After the collection, participants completed a 13-item questionnaire about their experience. Completed blood collection cards were mailed to the Michael T. Zuendel Family Biomarker Laboratory at Banner Sun Health Research Institute, where p-tau217 was measured using the Quanterix HD-X platform and compared to participants' p-tau217 result from Draw-10 venous samples.

Results: 49 participants were enrolled and attempted to provide a blood sample using 2 Capitainer SEP10 cards. 37(75.5%) participants were able to provide at least one usable blood card sample, such that the lab was able to extract sufficient plasma from the card to complete testing. p-tau217 measurements from the usable blood collection cards demonstrated a strong positive correlation with the venous samples from Draw-10 ($r=0.75$, $p<0.001$). Questionnaire data from participants and feedback from the study team noted almost all participants required assistance with the complex collection process, particularly related to slow bleeding, dexterity, and vision challenges of applying blood to the collection channels. 91.8% of participants reported the finger prick collection to be equally or less painful than a venous blood draw, 93.9% reported they were at least somewhat willing to use this collection method in the future for research studies, and 91.2% were at least somewhat willing to use finger prick cards for future medical or clinical tests as part of their personal healthcare needs.

Conclusions: The eDROP-AD study addresses the need for a simple, self-executable method of blood collection for measuring key AD biomarkers. While the blood collection cards used in this study had a strong positive correlation with the venous derived p-tau217 results, about 25% of participants were not able to provide a usable sample. Moreover, nearly all participants required assistance with the collection, suggesting that alternative card designs and/or collection methods are needed for real-world implementation of remote, self-collection of blood samples for AD biomarker testing. Additional studies are further exploring the comparability of different venous and capillary collections methods for the accurate measurement of AD biomarkers.

POSTER # 45

APOE E2 ATTENUATES TAU ACCUMULATION DESPITE ELEVATED AMYLOID RISK IN E4 CARRIERS. Li S, Protas H, Ghisays V, Lee W, Chen Y, Luo J, Devadas V, Sohankar J, Goradia D, Malek-Ahmadi M, Liang W, Woodruff B, Ashton NJ, Langbaum JB, Reiman EM, Su Y. Banner Alzheimer's Institute; Mayo Clinic Arizona; Banner Sun Health Research Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: Understanding how genetic risk factors influence amyloid and tau accumulation is critical for elucidating Alzheimer's disease (AD) progression. We implemented a continuous modeling framework to characterize the effects of Apolipoprotein E (APOE) genotype on amyloid and tau pathology using the Arizona APOE cohort. By leveraging sampled iterative local approximation (SILA) longitudinal trajectory modeling, we aimed to investigate allele-specific effects of APOE on biomarker trajectories.

Methods: We analyzed 343 cognitively unimpaired (ages 50-90) with 2- year PET scans of NAV and MK6240 tracers, processed using standardized pipelines. Logistic regression was used to assess baseline APOE effects on amyloid (A+) and tau (T+) positivity. Population-average amyloid trajectories were generated using the SILA model, and estimated amyloid onset age (EAOA) was calculated for participants with at least one A+ visit. Estimated tau onset time was derived using linear regression relative to amyloid chronicity.

Results: APOE e4 carriers (e2/e4, e3/e4, e4/e4) had significantly higher rates of A+ compared to e3/e3 individuals after adjusting for age and sex (p= III < 5%) across most genotypes, except e3/e4 and e4/e4. Notably, despite elevated amyloid positivity, e2/e4 individuals exhibited similarly low tau burden as e4 non-carriers. The estimated lag between amyloid onset (EAOA) and tau onset was highly variable but followed a consistent trend across regions: e2/e4 > e3/e3 > e3/e4 > e4/e4, indicating delayed tau emergence in e2/e4 carriers.

Conclusions: Our findings confirm the increased risk of amyloid and tau pathology associated with APOE e4. Importantly, the distinct biomarker profile observed in e2/e4 carriers suggests that while the e2 allele does not offset e4-related amyloid risk, it may attenuate downstream tau accumulation. These results highlight genotype-specific heterogeneity in AD progression and support further investigation into protective mechanisms associated with APOE e2

POSTER # 46

BDNF VAL66MET GATES SUSTAINED MEMORY ENHANCEMENT FOLLOWING INTERMITTENT THETA-BURST STIMULATION IN OLDER ADULTS WITH MILD COGNITIVE IMPAIRMENT. Liu Y, Sundman M, Green J, Chou Y. University of Arizona; Arizona Alzheimer's Consortium.

Background: Episodic memory decline is a hallmark of cognitive aging and early Alzheimer's disease; mild cognitive impairment (MCI) marks the prodromal stage. Intermittent theta-burst stimulation (iTBS), a patterned repetitive TMS protocol inducing long-term potentiation–like cortical plasticity, is a leading non-invasive candidate for enhancing memory-network function. Two questions remain central: durability of gains beyond the immediate post-stimulation window, and inter-individual variability in response. The brain-derived neurotrophic factor (BDNF) Val66Met polymorphism (rs6265) reduces activity-dependent BDNF secretion and affects synaptic consolidation and memory persistence, a strong candidate moderator of iTBS durability. We tested whether iTBS at a connectivity-guided individualized parietal target yields immediate and sustained memory enhancement in MCI, and whether Val66Met moderates this response.

Methods: Fifty-eight older adults with MCI completed a randomized, sham-controlled crossover trial of iTBS, continuous TBS (cTBS), and sham, counterbalanced with washout. The target was each participant's parietal region functionally connected to the left hippocampus (resting-state fMRI). Face–Name Associative Memory (FNAME) accuracy and d′ were primary outcomes, assessed pre-stimulation, post-stimulation (acute), and one-month follow-up (sustained). BDNF Val66Met was analyzed as Val/Val versus Met carriers (n = 20). Linear mixed-effects models tested protocol × timepoint × genotype interactions, covarying period and sequence. Connectome-based predictive modeling (CPM) related sham-controlled functional-connectivity change at two seeds (parietal site, left hippocampus) to behavioral change at each window. A cross-temporal analysis tested whether acute composites predicted sustained gains, testing BDNF moderation. Edges surviving leave-one-out cross-validation in >80% of folds were deemed robust.

Results: iTBS produced significant memory enhancement at one-month follow-up versus sham, surviving multiple-comparison correction. This benefit was driven by Val/Val carriers; Met carriers showed none, and a significant protocol × timepoint × genotype interaction confirmed BDNF moderation of durability. At the parietal site, two circuits subserved the effect: an acute circuit connecting to default-mode and medial-temporal targets (predictive in both genotypes), and a post-stimulation circuit shifting to anterior frontoparietal nodes—anterior cingulate, superior parietal, and dorsal-attention regions (predictive only in Val/Val carriers). At the left hippocampus, a core circuit (parahippocampal, posterior cingulate, inferior frontal, superior parietal regions) engaged at both windows; the sustained circuit also recruited anterior frontoparietal regions, and the BDNF gate emerged only at this expanded circuit. Cross-temporal prediction confirmed this: the same acute composites predicting immediate improvement in both genotypes predicted sustained benefit at one month only in Val/Val carriers.

Conclusions: BDNF Val66Met selectively gates the sustained, not the acute, memory-enhancement response to iTBS in MCI. The acute response engages memory-relevant circuits independently of genotype, but one-month durability requires BDNF-dependent late-phase plasticity, impaired in Met carriers. This identifies post-stimulation BDNF availability as a translational target, complementing stimulation-parameter optimization (individualized targeting, electric-field modeling, dose escalation). Translation may benefit from BDNF-genotype pre-stratification and co-interventions (aerobic exercise, pharmacotherapy) augmenting post-stimulation BDNF to rescue Met-carrier non-response. Replication in larger, balanced samples and direct tests of these maintenance-targeted strategies are priority next steps.

POSTER # 47

AMYLOID-PET CLASSIFICATION ACCURACY FOR ELECSYS COBAS P-TAU217 IN COGNITIVELY UNIMPAIRED OLDER ADULTS WITH EACH OF THE SIX COMMON APOE GENOTYPES. Malek-Ahmadi M, Devadas V, Li S, Protas H, Ghisays V, Denkinger MN, Singh A, Lee W, Chen Y, Luo J, Sohankar J, Goradia D, Liang W, Woodruff B, Langbaum JB, Reiman EM, Ashton NJ, Su Y. Banner Alzheimer's Institute; Banner Sun Health Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Plasma p-Tau217 is a currently approved for clinical tool to evaluate persons under the investigation of Alzheimer's disease (AD). In addition, in research settings, p-Tau217 can also accurately differentiate amyloid-positive from amyloid-negative cognitively unimpaired individuals. However, p-Tau217 classification accuracy across APOE genotypes has not been well established. In this study, we capitalized on the Arizona APOE Cohort, which includes cognitively unimpaired 50-90 year-old participants who were stratified for each of the six common APOE genotypes and age decile to characterize and compare the ability of the fully automated Roche Elecsys COBAS p-Tau217 to discriminate between amyloid PET-positive and negative in each of these genotypes.

Methods: p-Tau217 assays were on the Elecsys COBAS system using plasma samples from 314 cognitively unimpaired Arizona APOE Cohort participants, including 17 APOE2/2, 69 APOE2/3, 73 APOE3/3, 41 APOE2/4, 62 APOE3/4, and 42 APOE4/4 genotypes. Participants were 68.4±9.3 years old and had 16.6±2.1 years of education. 69% were female. ROC analyses using area under the curve (AUC) as well as sensitivity and specificity values (Sens, Spec) were used to assess the classification accuracy for amyloid-positivity (CL>20). Analyses within each genotype were carried out where the 2/2 and 2/3 genotypes were combined due to a small number of 2/2 carriers. Continuous and categorical (p-Tau217>0.189) analyses were carried out.

Results: Amyloid-positive prevalence was: 2/2=6%, 2/3=7%, 3/3=19%, 2/4=32%, 3/4=32%, 4/4=55%. Amyloid-positive cases had significantly higher p-Tau217 compared to amyloid-negative cases in all genotypes (p 0.189 cutoff was 90%/57% for the entire sample. Within-genotype Sens/Spec was (2/2+2/3=83%/53%, 3/3=93%/53%, 2/4=92%/36%, 3/4=84%/66%, 4/4=93%/66%).

Conclusions: The Elecsys COBAS p-Tau217 assay accurately identifies amyloid-positive persons. The classification accuracy was comparable across the 2/2, 2/3, 3/3, 3/4, 2/4, and 4/4 APOE genotypes. These findings underscore the assay's ability to identify cognitively unimpaired persons who have a high risk for progressing to clinical AD.

POSTER # 48

HEARING AGE: A SCALABLE ONLINE MEASURE OF HIGH-FREQUENCY HEARING HEALTH FOR AGING RESEARCH WITHIN THE MINDCROWD PLATFORM. Manna K, Venkatachalam H, Johnson M, Sharma S, De Both M, Alford K, Mendoza D, Schrauwen I, Huentelman M. University of Arizona College of Medicine – Phoenix; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Hearing loss is strongly associated with cognitive decline and increased risk for Alzheimer's disease (AD), but most hearing-cognition research depends on clinical audiometry and limiting scalability. Additionally, at larger scale, hearing is often investigated via self-reports or medical codes, overlooking the progressive nature of hearing that occurs with aging. The human hearing frequency range spans approximately 20 Hz to 20,000 Hz, though the upper limit of perceivable frequencies naturally decreases with age, making high-frequency hearing tests a useful measurement of overall hearing health. Here, we developed a new online test within the MindCrowd platform that estimates an individual's highest detectable frequency and offers a measure of hearing health relative to chronological age. We validate this test in the MindCrowd cohort on an initial group of 1049 participants and examine its association with population demographics. The test was designated as "Hearing Age".

Methods: Participants who completed the MindCrowd Hearing Age test, PAL memory test, and simple visual reaction time (svRT) test were included (N = 852, ages 19–88). The Hearing Age test employs three rounds of a linear frequency sweep (125 Hz–21 kHz over 60 seconds) preceded by a 500 Hz calibration step; participants indicate when they can no longer hear the ascending tone, yielding a highest detectable frequency for each round. Quality control removed invalid responses (20,100 Hz) and excluded rounds with high within-session variability (SD across rounds > 10 seconds). Linear regression tested predictors of hearing frequency (age, sex, and their interaction) with Type II ANOVA. All data analyses were conducted in R.

Results: After quality control, 92% of sessions (962/1049) were retained. Hearing frequency declined significantly with age ($\beta = -153$ Hz/year, $p < 2.2 \times 10^{-16}$), with age explaining ~50% of variance, validating the test's ability to capture expected audiometric patterns remotely. Males aged 60+ showed significantly worse hearing than females (−570 Hz, $p = 0.005$), with males declining ~47 Hz/year faster from midlife onward (age × sex interaction, $p = 0.009$ in 40+ subset). Self-reported hearing loss (−1,477 Hz, $p < 2.2 \times 10^{-16}$), tinnitus (−349 Hz, $p = 0.031$), and headphone type ($p = 9.3 \times 10^{-10}$) were significant predictors after adjusting for age and sex.

Conclusions: The MindCrowd Hearing Age test is a scalable online instrument that reliably captures age-related auditory decline and replicates established sex-differential hearing patterns in a community-based cohort. Additional work to be presented at the meeting will include: 1) comparing this test to a well-established online hearing test (speech-in-noise test) also integrated within the MindCrowd platform; 2) development of a predictive model of age ("hearing age") based on the current cohort; 3) investigation of the two hearing tests and differences between chronological age and predicted age based on hearing in relation to other assessments and self-reported measures within the MindCrowd platform, including memory performance and Alzheimer's disease risk. By embedding hearing assessment with the MindCrowd platform alongside memory and attention tests, this work establishes a foundation for longitudinal investigation of the hearing-dementia link at population scale.

POSTER # 49

ALTERED MIRNA EXPRESSION AND 3'UTR REGULATION OF PGRN AND TDP-43 EXPRESSION DURING THE INFLAMMATORY RESPONSE. Maqsood S, Lin J, Prince B, Harrison AM, Uppalapati CK, Leyva KJ, Hull EE. Midwestern University; Arizona Alzheimer's Consortium.

Background: Treatment with neuroprotective progranulin (PGRN) reduces lysosomal dysfunction and neuroinflammation associated with reduced PGRN levels. This therapeutic approach is particularly relevant; in frontotemporal dementia (FTD) as mutations in GRN (gene encoding PGRN) lead to (FTD-PGRN) and reduced PGRN levels due to mutations in Sortilin (SORT1), a PGRN trafficking receptor, are linked to increased risk for developing Alzheimer Disease (AD). Small RNA therapeutics may represent a targeted approach to boost PGRN levels and reduce pathology such as 1) the targeting of PGRN mRNA by multiple ncRNAs known to be upregulated in AD brain tissue and 2) the rs5848 polymorphism in the 3' UTR significantly influences PGRN in the serum and brain of AD patients. Indeed, strategies aimed at increasing PGRN levels have shown promise in pre-clinical studies and initial clinical trials. Currently, AAV-mediated therapies to increase PGRN levels with anti-Sortilin antibodies have been utilized. This work investigates an alternate approach, focusing on small RNA therapeutics to prevent GRN mRNA turnover, increasing PGRN expression. Given the multiple disease-associated links between TDP-43 binding to the 3' UTR of PGRN, the regulation of TDP-43 needs to be considered in parallel.

Methods: The ability of the inflammatory response to alter GRN expression via 3' UTR targeting was measured using luciferase reporter constructs transfected into microglial and neuronal cell lines. PGRN expression was reduced in both cell types, mimicking the disease state. Parallel experiments were performed using reporter constructs for TARDBP and GRN with the rs5848 polymorphism and after differentiation of neuronal lines. Alterations in ncRNA levels were evaluated by array methods to assess all small RNA levels. Immunoblots were used to assess alterations to PGRN levels after treatment.

Results: Pro-inflammatory cytokine treatment led to significant alterations in miRNA expression and increased signal from the GRN reporter construct, suggesting an increase in GRN expression in microglial and neuronal lines. In the neuronal line, TARDBP appeared to show an opposite effect. Interestingly, the effect of GRN 3'UTR regulation is abolished with the rs5848 polymorphism reporter construct, suggesting a regulatory role for miRNA659. Furthermore, reduction in endogenous GRN expression alters signal from the reporter construct suggestive of either competition from endogenous mRNA or a physiological effect which may contribute to pathology.

Conclusions: Our data suggest that expression of both the GRN and TARDBP genes may be significantly altered by miRNA during the inflammatory response. Additional experiments are needed to characterize the contribution of 3' UTR regulation to the expression of both genes and to assess the potential of small RNA therapeutics.

POSTER # 50

END-TO-END TRANSLATION OF FLUID BIOMARKERS FOR NEURODEGENERATIVE DISEASES: FROM DISCOVERY TO IMPLEMENTATION. Marques TM, Ghisays KL, Denkinger MN, Singh A, Shahub S, Ghisays V, Shakir S, Malek Ahmadi M, Hanley D, Atri T, Mazo L, Dieckhoff K, Liu J, Zuendel MT, Reiman EM, Ashton NJ. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Initiative To Change The D Word; The Sahlgrenska Academy At The University of Gothenburg; Arizona Alzheimer's Consortium.

Background: Fluid biomarkers are increasingly central to the early detection, stratification, and therapeutic monitoring of neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and related movement disorders. While advances in blood- and cerebrospinal fluid (CSF) biomarkers have accelerated translational progress, challenges remain across discovery, assay development, and implementation. The Fluid Biomarker Program at Banner Sun Health Research Institute was established to address these challenges through an integrated, end-to-end translational framework.

Methods: The Fluid Biomarker Program is a dedicated 3,200 sq ft facility comprising two specialized laboratories: the Michael T. Zuendel Family Biomarker Laboratory, focused on large-scale biomarker implementation, and the Kuhle Family Biomarker Discovery Laboratory, dedicated to biomarker discovery and assay development. Clinical-grade high-throughput analyses are performed using fully automated immunoassay platforms, including Cobas e801 (Roche Diagnostics), Lumipulse G1200 (Fujirebio), Atellica (Siemens Healthineers), and DxI 9000 (Beckman Coulter). Research discovery and assay development are supported by ultra-sensitive discovery platforms, including HD-X and SP-X (Quanterix), ARGO HT (Alamar Biosciences), Ella (Bio-Techne), and SPEAR (Spear Bio). Program activities focus on the development, validation, and large-scale measurement of plasma and cerebrospinal fluid protein biomarkers associated with neurodegenerative diseases, including tau, α-synuclein, TDP-43, and related pathologies, while supporting observational studies and clinical trials through assay standardization, cross-platform harmonization, and quality control workflows to ensure reproducibility and clinical readiness.

Results: Across multiple stages of biomarker translation, the program continues to demonstrate measurable progress. Since inception, the team has performed 225,214 high-throughput biomarker measurements supporting industry-sponsored studies, academic collaborations, large multicenter research initiatives, and federally funded programs, including the Alzheimer's Prevention Initiative (API) and SPRINT Trial. The laboratory is recognized as a major biomarker hub for international initiatives including Global Neurodegeneration Proteomics Consortium (GNPC), Alzheimer's Disease Neuroimaging Initiative (ADNI), Parkinson's Progression Markers Initiative (PPMI), and Global Parkinson's Genetics Program (GP2). Supported by the Michael J. Fox Foundation and Aligning Science Across Parkinson's, the program has expanded to develop blood biomarkers for Parkinson's Disease. Discovery proteomics using NULISA has identified blood signatures associated with postmortem-confirmed α-synuclein and TDP-43 pathology, while assays targeting tau eMTBR-243, HDGFL2 cryptic exon peptides, and other biomarkers are advancing toward scalable applications. Cross-platform evaluation of automated assays for phosphorylated tau and α-synuclein supports analytical validation and implementation, creating an integrated pipeline that accelerates biomarker translation for neurodegenerative disease research and therapeutic development.

Conclusions: The Fluid Biomarker Program represents a unique end-to-end translational ecosystem, enabling rapid movement from biomarker discovery to scalable assay development while driving the next generation of precision diagnostics for neurodegenerative disease research and clinical trials.

POSTER # 51

STORYTELLING, A NOVEL ASSESSMENT OF SEMANTIC NETWORKS IN OLDER ADULTS.

Mazurik G, Edmonds EC, Rapcsak S, Grilli MD. University of Arizona; Arizona Alzheimer's Consortium.

Background: Whereas semantic memory is largely stable in healthy older age, several aspects of semantic cognition are impaired in individuals with mild cognitive impairment (MCI). Prior literature has used semantic memory assessments such as naming tasks or generative retrieval tasks to assess lexical access and crystalized intelligence, and to compare cognitively healthy older adults to those who have MCI. Despite these cognitive processes playing a part in semantic memory, these traditional assessment measures do not capture all aspects of semantic cognition such as semantic novelty and control. In the present work, we aim to assess semantic novelty and control through a verbal storytelling task that involves activating conceptual nodes that are distant from a prompting concept.

Methods: Our preliminary study will focus on assessing cognitively healthy older adults (60-89). Participants are asked to create a fictional narrative utilizing details that are given to them such as the name and occupation of a fictional main character, a setting for the story, and a sentence that illustrates how the character's story comes to an end. Using Latent Semantic Analysis (LSA) we plan on quantifying the semantic details of story responses to assess participants' amount of semantic novelty and control, with the assumption that individuals with better semantic novelty and control have a wider, more robust access to their semantic network.

Results: We hypothesize that our verbal storytelling task will reveal age effects and individual differences in semantic cognition, beyond those captured by traditional assessment methods. The results will be presented and discussed.

Conclusions: Ultimately, this approach may help develop a novel method of characterizing semantic networks in older adults who vary in their cognitive status.

POSTER # 52

BRAIN GAMES? ASK ME: PILOTING A BRAIN HEALTH AMBASSADOR AND KIOSK PROGRAM IN NORTHERN ARIZONA. McCoy M, Cerino E, German P, Shannon F, Fleury K, Dopson R, Duong D, Lucero L, McCarthy M. Northern Arizona University; Joe C. Montoya Community & Senior Center; Arizona Alzheimer's Consortium.

Background: Arizona has experienced a 33% increase in Alzheimer's disease (AD) prevalence since 2020, the largest percentage increase in the country. The burdens of AD are exacerbated for people living in rural social contexts in Northern Arizona, Tribal Nations, and across the US who experience geographic barriers to memory care. These memory care deserts often lack AD care resources designed to support people with cognitive impairment and their caregivers. The purpose of this study is to describe initial piloting steps for a new Brain Health Ambassador and Kiosk Program co-developed in partnership with a local community center in Northern Arizona.

Methods: The Brain Health Ambassador and Kiosk Program is a new initiative from the Northern Arizona Memory Study (NAZMS) designed to couple technology with peer support to create and share brain health resources in rural community centers across Northern Arizona. Currently being piloted with the Joe C. Montoya Center in Flagstaff, AZ, NAZMS team members trained and co-designed resources with "Brain Health Ambassadors", older patrons of the local community center. Trainings consisted of brain health education, technology assistance, and discussions on how to best create accessible resources.

Results: Montoya Center's pilot Brain Health Kiosk was introduced in April 2026 as part of a NAZMS Brain Health Fair (n=36 attendees). The majority of attendees engaged with the Brain Health Ambassadors and/or the Brain Health Kiosks. 100% of Brain Health Fair attendees indicated that they "learned about community resources related to brain health". 54% participated in brain health games, 85% attended a brain health presentation, 62% talked with community table representatives, and 38% used the Brain Health Kiosks. Kiosk users indicated (i.e., "somewhat agree" or "agree") that, "As a result of using the Brain Health Kiosk, they were… "able to find the information they needed" , "learned information about brain health that they will share with others" , and "felt more knowledgeable about brain health," with suggestions for improvement including better accessibility for individuals with low vision and simplified navigation. In total, 9 Brain Health Fair attendees were screened for AD risk.

Conclusions: NAZMS plans to continue using the Montoya Center Brain Health Kiosk as a pilot to learn, refine, and ultimately develop a toolkit for replication in other centers throughout Northern Arizona. This Brain Health Ambassador and Kiosk Program directly aligns with Arizona's State Plan for AD through improved outreach and offerings of brain health promotion, cognitive screenings, and dementia risk reduction strategies across rural communities in Northern Arizona.

POSTER # 53

ENHANCING LYSOSOMAL ACTIVITY AS A THERAPEUTIC MODALITY FOR NEURODEGENERATIVE DISEASES. Mercer RCC, Le NTT, Whetzel A, Stephens HR, Mirza-Romero NA, Orbe IC, Flaherty E, DeFranco JP, Lavigna G, Gatdula JRP, Fraser DG, Sundaravadivelu A, Vultaggio JS, Haley NJ, Beeler AB, Chiesa R, Telling GC, Harris DA. Midwestern University; The Ohio State University; Colorado State University; Istituto Di Ricerche Farmacologiche Mario Negri IRCCS; Boston University; Midwestern University; Arizona Alzheimer's Consortium.

Background: Prion diseases are fatal neurodegenerative diseases of humans and other mammals with no current treatment options. A lack of mechanistic insight into the activity of many anti-prion compounds has hampered identification of small molecules with efficacy in patients. Solving this problem has broad implications, since common cellular pathways are believed to underpin classical prion diseases and other more common protein misfolding neurodegenerative conditions. Activation or restoration of lysosomal function using small molecules has recently gained attention as a novel therapeutic modality.

Methods: Immortalized and primary cell culture, western blot, Real Time Quaking Induced Conversion (RT-QuIC) assay, scrapie cell assay, CRISPR/Cas9, immunofluorescence, RNA-seq, functional fluorescent probes of lysosomal activity.

Results: We discovered that elacridar, a third-generation inhibitor of MDR1/p-glycoprotein/ABCB1, prevents PrP-prion propagation and synaptotoxicity at submicromolar concentrations in vitro. Elacridar acts at an early step in the prion infection process, enhancing degradation of newly formed PrPSc. Transcriptomic analysis and the use of functional lysosomal probes implicate lysosomal processes in these anti-prion effects. Elacridar alters gene expression networks controlling lysosomal sterol and lipid metabolism but, unlike other lysosomotropic drugs, it prominently upregulates genes that control lysosomal pH. Surprisingly, these effects occur independently of TFEB nuclear translocation, suggesting novel regulatory mechanisms. Importantly, the inhibitory effects of elacridar extend to the seeding activity of prions composed of alpha-synuclein and tau.

Conclusions: Our findings highlight lysosomal enhancement as a general strategy for treatment of protein misfolding neurodegenerative diseases. There is now a major effort to identify drugs that act via this mechanism, and our work positions elacridar as an important new addition to this growing field.

POSTER # 54

DIABETES IS INDEPENDENTLY ASSOCIATED WITH BRAIN ATROPHY AMONG PATIENTS WITH CAROTID ARTERY STENOSIS. Nelson C, Zhang, H, Ugonna C, Trouard T, Chou Y, Hsu CH, Zhou W. University of Arizona; Arizona Alzheimer's Consortium.

Background: Carotid artery stenosis and diabetes mellitus have both been associated with structural neurodegeneration and cognitive dysfunction, yet the interactions between these comorbid conditions remains poorly characterized. This study aims to examine the impact of diabetes on brain structure among a cohort of patients undergoing treatment for severe cervical carotid artery atherosclerotic disease.

Methods: Subjects who were enrolled in a longitudinal study on the cognitive effects of microembolization associated with carotid intervention (NIH R01NS070308) were included in this retrospective analysis. Volume (mm3) and cortical thickness (mm) were measured from high-resolution baseline T1 brain MRI and normalized against total brain volume using FreeSurfer, an open-source, neuroimaging analysis platform. Linear mixed-effects models were then used to assess associations between diabetes status and brain measures and to account for within-subject dependency. False discovery rate correction was also applied using the Benjamini-Hochberg method.

Results: Brain MRI data from 125 patients were obtained and included in the analysis, among which 47 (37.6%) patients were diabetic. The diabetic cohort had a higher mean hemoglobin A1c (7.5 vs 5.8, $p< 0.05$). There was a robust association ($p < 0.05$) between diabetes and low insula volume and posterocingulate volume, as well as orbitofrontal and lateralorbitofrontal thickness, temporal lobe thickness, supramarginal parietal thickness, and insula thickness. White matter volume did not vary by diabetes status after FDR correction.

Conclusions: Among patients with carotid artery stenosis, diabetes is associated with reduced global gray matter volume and widespread cortical thinning, most prominently in the temporal lobe, insula, and cingulate cortex. These data are suggestive that diabetes is associated with structural neurodegeneration beyond that of carotid artery stenosis alone and may also contribute to cognitive decline in populations with these comorbid conditions.

POSTER # 55

STRATEGIC SELF-CUEING AND BRAIN STIMULATION AS A COMBINED INTERVENTION FOR WORD-FINDING DEFICITS IN SEMANTIC VARIANT PPA. Nickels K, Lopez IA, Kuawu A, Kielar A. University of Arizona; Arizona Alzheimer's Consortium.

Background: Individuals with the semantic variant of primary progressive aphasia (svPPA) experience severe deficits in word-finding abilities associated with neurodegeneration of the anterior temporal lobes. Previous studies have documented that speech-language intervention can improve naming skills in those with svPPA; however, treatment effects are often limited to trained items, and maintenance of gains is variable. The purpose of this study was to examine the therapeutic value of a modified Lexical Retrieval Cascade Treatment (m-LRCT), an approach that trains semantic, phonological, and orthographic self-cueing strategies to improve word retrieval, paired with transcranial direct stimulation (tDCS). In other treatment contexts for progressive aphasia, tDCS has been shown to augment the effects of speech-language therapy by improving generalization and maintenance effects.

Methods: We investigated the effects of m-LRCT coupled with anodal tDCS of the left prefrontal gyrus in a single participant with svPPA (SV38). On baseline assessment, SV38 demonstrated deficits in confrontation naming (51.7% accuracy), single-word comprehension (72.4% accuracy), and nonverbal semantic association (70.3% accuracy) relative to a group of age and education-matched controls (*p*s <.001). During treatment, m-LRCT strategies were trained using five sets of five untrained words (matched on relevant psycholinguistic variables) with corresponding picture cards. Treatment sessions took place every weekday for two weeks, with follow-up testing after two months. An item-by-item analysis was performed on assessment task scores before and after treatment and at follow-up using McNemar tests.

Results**:** Following treatment, SV38 demonstrated improvement on the 25 untrained probes items (0% to 92%), p <.001, and these gains were maintained to the two-month follow-up testing timepoint (92%), p <.001. Performance on untrained probes and the Boston Naming Test improved numerically immediately after treatment (+7.1% and +6.6%, respectively), but these changes were not significant. However, at follow-up, performance on the Boston Naming Test had improved to 66.7% (+15% from pre-treatment), p = 0.012. Scores on tests of nonverbal semantic association remained stable over the course of the study, but SV48 improved by +12.5% on a test of single-word comprehension after treatment, approaching significance, p = 0.063. When asked about the functional impact of therapy, SV48 rated her word-finding abilities and ability communicate during daily conversions as "much better" after treatment.

Conclusions: There is urgency to develop robust protocols for individuals living with progressive language loss, and these data present encouraging evidence regarding the approach that targets strategic self-cueing, coupled with tDCS, in svPPA. Our participant demonstrated improved word-finding for trained items that generalized to untrained words and single-word comprehension skills. Importantly, these changes reflected a positive impact on SV48's functional communication skills for everyday life.

POSTER # 56

DIVERGENT NEURONAL DYSREGULATION AND SEX-BIASED GLIAL EXPRESSION DIFFERENTIATE LEWY BODY AND ALZHEIMER'S DISEASE PATHOLOGY. Olney K, Rabichow B, DeTure M, McLean P, Dickson D, Chang R, Ross O, Fryer J. Translational Genomics Research Institute; Mayo Clinic Arizona; Mayo Clinic Florida; University of Arizona; Arizona Alzheimer's Consortium.

Background: Dementia affects 57 million globally, with Lewy body disease (LBD) and Alzheimer's disease (AD) being among the leading causes of neurodegenerative dementia over the age of 65. LBD and AD can exhibit clinicopathological overlap, complicating diagnosis and treatment. A key knowledge gap concerns the molecular alterations that distinguish LBD from AD.

Methods: We performed single-nucleus RNA sequencing of the anterior cingulate cortex from 35 neuropathologically defined human brains, selected to represent a spectrum of Thal amyloid-β phase (A), Braak tau neurofibrillary tangle stage (T), and α-synuclein inclusions (S). The cohort was stratified into five groups: Control (n=7), AD (AT, n=8), LBD (S, n=7; AS, n=7; ATS, n=6). We classified 353,350 nuclei into major cell types and conducted pairwise differential gene expression analyses. To detect coordinated expression patterns linked to disease, quantitative neuropathological burden, age, and biological sex, we used high-dimensional weighted gene co-expression network analysis (hdWGCNA).

Results: Our analysis revealed unique, divergent gene expression patterns in excitatory neurons that distinguish LBD from AD. LBD (S) cases upregulated genes linked to proteostasis and Parkinson's pathways. In contrast, mixed-pathology LBD (AS) and LBD (ATS) cases uniquely downregulated genes related to ribonucleoprotein (RNP) complex biogenesis and synaptic vesicle transport, indicating diminished synaptic transcription as pathology diversifies. hdWGCNA identified an excitatory neuronal gene module linked to calcium-lipid signaling that was consistently downregulated across the AD-LBD spectrum, suggesting that diminished neuronal signaling is common to both LBD and AD. In glial cell types, we found downregulation of gene modules related to astrocyte signaling, microglial homeostasis, oligodendrocyte myelination, and oligodendrocyte progenitor cell (OPC) structural support. We also observed a conserved increase in stress and proteostasis gene modules across glial cells, marked by heat shock proteins and chaperone genes. The activation of these stress-response gene modules was strongly linked to Lewy body pathology in males but remained static in females, indicating sex differences in glial responses to protein aggregation.

Conclusions: Identifying cell-type- and sex-specific transcriptional signatures highlights the potential for precise biomarkers, enabling earlier diagnosis, improved disease classification, and targeted therapies tailored to neuropathological burden and sex.

POSTER # 57

NORPSILOCIN ATTENUATES APOPTOTIC SIGNALING AND PROMOTES NEUROPROTECTION IN CELLULAR MODELS OF PARKINSON'S DISEASE. Ordovich-Clarkson RD, Jabbour M. Grand Canyon University.

Background: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by alpha-synuclein aggregation, mitochondrial dysfunction, oxidative stress, and progressive loss of dopaminergic neurons. Although current therapies improve motor symptoms, they do not prevent the underlying neurodegenerative process, highlighting the need for disease-modifying strategies. Norpsilocin, a serotonergic five-hydroxytryptamine 2A (5-HT2A) receptor agonist and structural analog of psilocin, has emerged as a promising candidate due to its reported neuroplastic and neuroprotective properties. While serotonergic compounds have demonstrated beneficial effects in models of neuronal injury, the molecular mechanisms by which norpsilocin influences neuronal survival and apoptotic signaling remain poorly understood. The present study investigated whether norpsilocin promotes neuroprotection by modulating apoptotic pathways and neurotransmitter-related gene expression in cellular models of Parkinson's disease.

Methods: Differentiated SH-SY5Y human neuroblastoma cells were used as an in vitro model of Parkinson's disease. Cellular injury was induced through oxidative stress and followed by treatment with norpsilocin. The neuroprotective effects of norpsilocin were evaluated using complementary cellular and molecular approaches. Cell viability was assessed by MTT assay, while expression levels of apoptotic proteins (BAD, p-BAD, BAX, and PUMA) were assessed via western blotting. Gene expression levels were analyzed using real time-quantitative polymerase chain (PCR) using apoptosis- and neurotransmitter-related gene panels. Together, these complementary assays were used to characterize the effects of norpsilocin on neuronal viability, apoptotic signaling, and molecular pathways relevant to neurodegeneration.

Results: Norpsilocin treatment consistently promoted neuroprotective signaling across multiple experimental platforms. MTT assays demonstrated improved cellular viability, while western blot analysis revealed increased expression of phosphorylated BAD with reduced expression of BAD indicating attenuation of intrinsic apoptotic signaling. Quantitative polymerase chain reaction further demonstrated transcriptional changes consistent with enhanced neuronal survival, including modulation of apoptosis-related genes and neurotransmitter-associated pathways involved in inhibitory neurotransmission, synaptic organization, and cholinergic signaling. Collectively, these findings suggest that norpsilocin promotes cell survival through coordinated regulation of apoptotic and neurotransmission-related molecular pathways.

Conclusions: These findings provide preliminary evidence that norpsilocin promotes neuroprotective signaling in cellular models of Parkinson's disease through coordinated modulation of apoptotic pathways and neurotransmitter-related gene expression. By integrating measures of cell viability, protein expression, and transcriptional regulation, this study offers mechanistic insight into the potential therapeutic effects of norpsilocin beyond symptomatic treatment. Although additional studies are needed to validate these findings in vivo and further characterize the underlying molecular pathways, the present work supports continued investigation of norpsilocin as a promising candidate for disease-modifying strategies in Parkinson's disease and related neurodegenerative disorders.

POSTER # 58

PERFORMANCE OF PLASMA P-TAU217 TO DETECT ALZHEIMER'S PATHOLOGY IN A CLINICAL COHORT WITH LOGOPENIC PRIMARY PROGRESSIVE APHASIA. Pacheco D, Crisler Kearney AS, Edmonds EC, Menchola M, Rapcsak SZ. Midwestern University; Banner Alzheimer's Institute – Tucson; University of Arizona; Arizona Alzheimer's Consortium.

Background: Logopenic variant primary progressive aphasia (lvPPA) is a progressive language disorder characterized by word-finding difficulties, impaired sentence repetition, and phonological paraphasic errors. Imaging studies (MRI/FDG PET) typically show left temporoparietal atrophy/hypometabolism. In the majority of cases lvPPA is associated with Alzheimer's disease (AD) pathology, based on postmortem studies, CSF biomarkers, and amyloid/tau PET imaging. However, it is well documented that in a subset of patients with the clinical phenotype of lvPPA, amyloid PET imaging is negative; in these cases it is assumed the syndrome is caused by non-AD pathologies (e.g., TDP-43, tau, or alpha synuclein). Although plasma p-tau217 has shown high sensitivity and specificity for AD pathology, the association between p-tau217 and lvPPA has not been systematically studied. Our study examined the performance of p-tau217 to identify AD pathology in a memory disorders clinic sample of patients with lvPPA.

Methods: We conducted a retrospective review to identify individuals diagnosed with lvPPA by a behavioral neurologist at BAI–Tucson who also had p-tau217 results. Plasma p-tau217 analyses were conducted with the Fujirebio Lumipulse® essay. Test positivity was determined using both single and dual cutoff methods. We also reviewed MRI, FDG PET, amyloid PET, CSF biomarker, and APOE genotype data when available.

Results: Twenty-two patients (mean age=76.1) with a lvPPA diagnosis had p-tau217 results (mean=1.07 pg/mL). Using a single cutoff (>0.185 pg/mL), all 22 patients were classified as p-tau217 positive; using a dual cutoff, 21 patients were positive (>0.325 pg/mL) and 1 was intermediate (0.186–0.324 pg/mL). All patients had structural MRI results; 15 showed asymmetrical left temporoparietal atrophy. Ten patients had FDG PET scans; all showed either left or bilateral temporoparietal hypometabolism. Ten patients had amyloid PET scans; 6 were positive. Three of the 4 amyloid PET negative patients had positive CSF biomarkers for AD. P-tau217 levels were comparable between amyloid PET positive vs. negative cases. Ten patients had APOE results; 7 (4 amyloid PET negative and 3 positive) had e3/e3 genotype. Of the other 3 patients (2 amyloid PET positive), 2 were heterozygotes and 1 homozygote for APOE e4.

Conclusions: In our clinical cohort of lvPPA patients, p-tau217 testing confirmed the high prevalence of AD pathology. Plasma p-tau217 was highly positive even in amyloid PET negative cases that are typically assumed to have non-AD pathology. Our findings suggest that in some cases of lvPPA due to AD, hyperphosphorylation of tau can trigger accumulation of tangle pathology and subsequent neurodegeneration in the posterior temporoparietal components of the language network in the absence of amyloid plaque burden measurable by PET.

POSTER # 59

MITOCHONDRIAL METABOLIC UPREGULATION IN THE FRONTAL CORTEX IN VERY OLD INDIVIDUALS WITH SUPERIOR COGNITIVE ABILITIES. Perez S, He B, Malek-Ahmadi M, Mufson E. Barrow Neurological Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Superagers are an exceptional group of adults aged 80 years and older whose episodic memory performance surpasses that of age-matched peers and remains comparable to individuals 20-30 years younger. Although numerous studies have highlighted the central role of mitochondria in longevity and healthy aging, the mitochondrial function in the preservation of exceptional memory in these very old individuals remain largely unexplored. Here, we investigated mitochondrial metabolism in the frontal cortex (FC) of non-demented individuals aged 80 years and older whose episodic memory performance was superior to that of normal cognitive performers.

Methods: Participants were identified from the Rush Religious Orders Study (RROS) using our recently published psychometric criteria based on the last available Wechsler Memory Scale-Revised Logical Memory Delayed Recall (LM-DR) score obtained prior to death. Levels of proteins associated with mitochondrial biogenesis (PGC-1α, NRF1, NRF2, TFAM, Sirtuin 1), mitophagy (FUNDC1, BNIP3L/NIX, DRP1), energy production (lactate dehydrogenase A [LDHA] and B [LDHB]), and calcium signaling (BAP31, VDAC1, MFN2, GRP75, PTPIP51), all critical regulators of mitochondrial homeostasis known to decline with aging, were assessed in the FC of 22 superior cognitive performers (SCP; LM-DR ≥14) and 17 normal cognitive performers (NCP; LM-DR 7-13) using western-blot.

Results: Compared with NCP, SCP exhibited significantly higher levels of the mitochondrial biogenesis proteins NRF1 (Mann-Whitney test, $p = 0.0002$), NRF2 ($p = 0.004$), and Sirtuin 1 ($p = 0.04$), whereas PGC-1α and TFAM levels were unchanged. The mitophagy receptor BNIP3L/NIX was significantly elevated in SCP ($p = 0.003$), while FUNDC1 and the mitochondrial fission protein DRP1 showed no group differences ($p > 0.05$). Levels of LDHA ($p = 0.002$) and LDHB ($p = 0.01$) were significantly increased in SCP, although the LDHA/LDHB ratio remained unchanged. Among proteins associated with mitochondria-associated membranes, key in calcium transferring, MFN2 ($p = 0.001$) and GRP75 ($p = 0.02$) were significantly upregulated in SCP, whereas BAP31, VDAC1, and PTPIP51 levels did not differ between groups ($p > 0.05$). Correlation analyses revealed significant positive associations between LM-DR scores and NRF1 (Spearman $r = 0.55$, $p = 0.001$) and NRF2 ($r = 0.46$, $p = 0.006$) across cognitive groups. Episodic memory performance was also positively correlated with NRF1 ($r = 0.45$, $p = 0.009$) and MFN2 ($r = 0.53$, $p = 0.001$). In contrast, BNIP3L/NIX levels were negatively correlated with Braak stage ($r = -0.83$, $p = 2 \times 10^{-7}$) and total neurofibrillary tangle burden ($r = -0.65$, $p = 0.004$).

Conclusions: These findings suggest that enhanced mitochondrial function is a key mechanism supporting the maintenance of exceptional cognition during advanced aging.

POSTER # 60

PLASMA BRAIN DERIVED P-TAU217 PREDICTS FUTURE TAU PET ACCUMULATION.
Protas HD, Denkinger MN, Ghisays V, Singh A, Li S, Luo J, Sohankar J, Chen Y, Goradia DD, Malek-Ahmadi M, Lee W, Devadas V, Reiman EM, Ashton NJ, Su Y. Banner Alzheimer's Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Plasma p-tau217 is a leading blood based biomarker for Alzheimer's disease (AD), yet its temporal relationship to tau PET remains unclear. Determining whether circulating p-tau217 captures tau pathology earlier than PET is central to disease staging, therapeutic targeting, and clinical trial design. We evaluated whether brain derived p-tau217 (BD-pTau217) associates with and predicts tau PET burden across disease stages.

Methods: BD-pTau217 from the NULISA CNS panel was quantified in 1,427 ADNI participants (223 AD, 675 MCI, 529 CU). A longitudinal subset (41 impaired, 53 CU) underwent FTP PET scanning, with the first scan 2.8 ± 2.9 years from plasma baseline and follow up imaging ~2.0 ± 0.2 years later. Tau PET metrics included entorhinal and metatemporal SUVR, and tau network strength derived from cross-sectional data. Predictive models evaluated whether BD-pTau217 predicted 2 year tau PET outcomes, adjusting for baseline tau, age, sex, diagnosis, and plasma-to-PET interval. Linear mixed-effects models further assessed whether BD-pTau217 predicted individual trajectories of tau accumulation. Mediation analyses tested whether BD-pTau217 statistically mediates the association between amyloid PET and subsequent tau accumulation.

Results: At baseline, tau network strength showed the strongest associations with BD-pTau217($\rho \geq 0.49, p = 9\times10^{-7}$), exceeding those observed for SUVR($\rho \leq 0.47$, $p = 2.7\times10^{-7}$). In CU individuals, BD-pTau217 correlated with metatemporal strength($\rho = 0.46$, $p = 6\times10^{-4}$) and entorhinal SUVR ($\rho = 0.42$, $p = 0.002$). Associations with future tau PET were consistently stronger than with baseline tau PET. BD-pTau217 predicted longitudinal increases in all tau metrics except entorhinal strength ($p < 10^{-16}$).

Conclusions: BD-pTau217 shows robust cross-sectional relationships with tau PET and stronger associations with tau PET measured years later, consistent with a temporally upstream role relative to PET detectable tau spread. Its ability to predict future tau PET independent of baseline pathology, combined with evidence supporting a mediating role between amyloid and tau accumulation, positions BD-pTau217 as a key transitional biomarker in the AD pathological cascade. These findings support BD-pTau217 as an early, biologically meaningful indicator of tau propagation with strong potential for early detection, staging, and therapeutic trial enrichment.

POSTER # 61

ACUTE EFFECTS OF EXERCISE, WITH AND WITHOUT ANTI-AMYLOID THERAPY, ON FLUID BIOMARKERS IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT. Racette SB, Gunning JA, Converse MF, Gudarzi B, Aliskevich EL, Sabbagh MN. Arizona State University; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: The primary pharmacological strategy to slow the progression of mild cognitive impairment (MCI) to dementia is monoclonal antibody therapy that reduces amyloid beta protofibrils and amyloid beta plaque. An important lifestyle strategy to optimize neurological health is aerobic exercise; exerkines released in response to exercise are signaling molecules that stimulate a cascade of important metabolic effects. The knowledge gap addressed by this study is whether there are complementary and/or synergistic physiological effects of exercise added to anti-amyloid therapy on fluid biomarkers relevant to neurogenesis and neurodegeneration. The aims are 1) to evaluate the acute effects of aerobic exercise, independently and when combined with anti-amyloid therapy, on physiological pathways that impact amyloid beta deposition in patients with MCI and 2) to explore the time course of blood biomarker concentrations for 48 hours following acute exercise in patients with MCI, with and without anti-amyloid therapy.

Methods: This is a cross-sectional pilot study of patients aged 60-90 y with amyloid positivity and MCI in two groups: those receiving anti-amyloid therapy for ≥6 months and those not receiving anti-amyloid therapy. A single treadmill exercise bout was performed (30-min at 60-75% of age-predicted maximal heart rate) and blood biomarkers were obtained at 5 time points: before exercise and 0 min, 60 min, 24h, and 48h post exercise. Blood biomarkers include brain-derived neurotrophic factor (BDNF), beta-hydroxybutyrate, beta-secretase, cathepsin B, glucose, inflammatory cytokines, irisin, lactate, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 alpha), and vascular endothelial growth factor (VEGF).

Results: Fourteen participants completed the study (7 on anti-amyloid therapy | 7 not on anti-amyloid therapy); baseline characteristics did not differ between groups. The overall sample was 57.1% male with a mean age of 75.9 y (SD 5.4, range 64-86 y), BMI 26.7 (4.9) kg/m2, MoCA score 19.6 (6.0), Trail Making A score 65 (32) seconds, Trail Making B score 131 (96) seconds, six-minute walk distance 489 (94) meters, and short physical performance battery score 10.4 (SD 1.5, range 7-12; highest/best score is 12). Exercise intensity during the treadmill test was 68.5 (3.3) % of age-predicted maximal heart rate. Blood biomarker analyses are ongoing and will be completed in summer 2026; statistical analyses will reveal the time course of biomarkers over 48h and explore differences by anti-amyloid treatment group.

Conclusions: Results of this study will provide novel and important preliminary data on metabolic pathways that are responsive to aerobic exercise in patients with amyloid positivity and MCI who are receiving anti-amyloid therapy and whether this differs from patients not receiving anti-amyloid therapy.

POSTER # 62

EVALUATING POLYGENIC RISK SCORES TO PREDICT ALZHEIMER'S AND AMYLOID POSITIVITY IN AN ELECTRONIC HEALTH RECORD. Robb WH, Kaur GK, Conyers CT, Bouchal SM, Greig EE, Upjohn DP, Grilli CB, Ortega VE, Hohman TJ, Vemuri P, Ramanan VK, Koran MEI. Mayo Clinic Arizona; Mayo Clinic Florida; Vanderbilt University School of Medicine; Mayo Clinic Rochester; Arizona Alzheimer's Consortium.

Background: The emergence of anti-amyloid therapies has created an urgent need for scalable strategies to identify patients most likely to develop Alzheimer's disease (AD) and amyloid-β positivity before symptom onset. While polygenic risk scores (PRS) offer promise for precision medicine and trial enrichment, their predictive performance across real-world EHR populations, varying phenotype definitions, and distinct APOE genotype backgrounds remains incompletely characterized.

Methods: We evaluated 55 AD PRS from the PGS Catalog in 109,933 individuals aged ≥50 years across two EHR-linked cohorts (Mayo Clinic Biobank, Tapestry). PRS performance was assessed across a gradient of clinical and biomarker-confirmed phenotypes, ranging from broad ICD-derived diagnoses to confirmed amyloid positivity (Aβ+). We separated APOE from the non-APOE polygenic background and tested main and interaction effects of PRS with APOE ε4 and ε2 dosage.

Results: In fixed-effects meta-analyses, the PRS derived from the "2026 Consensus meta-analysis" consortia GWAS demonstrated the highest discriminative performance (Aβ+ vs. ICD-controls: AUC=0.80, OR=1.55 [1.40-1.71]). PRS effect sizes and predictive accuracy increased monotonically with greater phenotype specificity, from ICD-defined dementia to ICD-defined AD to Aβ+ status. In time-to-event models, both APOE and polygenic risk independently contributed to AD risk, with hazard ratios (HR) of 3.25 (95% CI: 2.98–3.54) per APOE ε4 allele and 1.43 (1.36–1.51) per SD increase in PRS, while ε2 conferred protection (HR=0.66, 0.55–0.79). Evidence for ε4×PRS interaction was weak, whereas ε2 dose attenuated PRS associations, most notably for Aβ+ outcomes (interaction HR=0.58, 95% CI: 0.39–0.85, FDR p=0.030).

Conclusions: The best-performing AD PRS in this EHR-linked population was derived from the most recent large-scale GWAS, and PRS performance improved as phenotype definitions became more biologically specific. Non-APOE polygenic risk added meaningful information beyond APOE genotype, supporting its use for genetic enrichment in amyloid screening and AD prevention trials. Furthermore, the observation that the APOE ε2 allele attenuates polygenic risk highlights a potential resilience mechanism that warrants further investigation.

POSTER # 63

APOE4 ASSOCIATION WITH AMYLOID BETA AND WHITE MATTER HYPERINTENSITY: A MEDIATION ANALYSIS. Saidi P, Cramer J, Zhou Y, Baxter L, Su Y, Woodruff B, Caselli R, Dumkrieger G, Dumitrascu O. Mayo Clinic Arizona; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Automated white matter hyperintensity (WMH) segmentation and quantification enable systematic investigation of APOE4 allelic dosage association with WMH burden and amyloid-beta positivity.

Methods: In a cross-sectional single-institution cohort including 153 cognitively intact participants (13 APOE4 homozygotes, 50 heterozygotes, 90 non-carriers), an image analysis pipeline was used to quantify global and regional WMH volumes from T1-weighted and T2-FLAIR scans. The effects of APOE4 on WMH burden and WMH burden on amyloid-PET were tested using linear and logistic regression models.

Results: APOE4 carriers had non-significantly greater WMH volumes compared to non-carriers, whereas APOE4 homozygotes exhibited significantly greater WMH volumes compared to non-carriers, particularly in the posterior periventricular area ($p=0.002$, $d=0.948$). WMH burden was not associated with amyloid-beta positivity (odds ratio=1.18, $p=0.718$).

Conclusions: Although WMH was greater in APOE4 homozygotes, it did not mediate the relationship between APOE4 and amyloid-beta positivity in cognitively normal individuals.

POSTER # 64

COMPARATIVE PERFORMANCE OF PLASMA PTAU217 AND MRI FEATURES IN PREDICTING AMYLOID-B POSITIVITY PRECLINICALLY USING EXPLAINABLE MACHINE LEARNING. Saidi P, Cramer J, Zhou Y, Baxter L, Su Y, Woodruff B, Caselli R, Dumkrieger G, Dumitrascu O. Mayo Clinic Arizona; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Plasma pTau217 can predict amyloid-β. However, its performance is reduced within an intermediate range. An explainable ML model is developed using MRI-derived features in cognitively normal individuals to improve prediction performance in cases where pTau217 is less informative.

Methods: 65 cognitively intact individuals were included. 20 were amyloid-β positive (amyloid–PET centiloid unit > 20; 11 in pTau217 high-risk, 1 in low-risk and 8 in the intermediate range) and 45 amyloid-β negative (3 in pTau217 high-risk, 37 in low-risk and 5 in the intermediate range). Three models were developed. First model was trained using only pTau217. Second model was trained using MRI-based features (3D T1-weighted and T2- FLAIR), age and APOE ε4 status. Third, an ensemble model was developed to integrate the two models. Shapley analysis was used for post-hoc interpretations.

Results: The ML model trained using only pTau217 achieved an area under the curve (AUC) of 0.885±0.01 and sensitivity of 0.855±0.07 and specificity of 0.834±0.02. Performance decreased in the intermediate subgroup with AUC of 0.325±0.09. The imaging-based model showed lower overall performance (AUC of 0.696±0.04), however, improved performance in the intermediate subgroup (AUC=0.629±0.07). SHAP analysis identified age, APOE ε4 and white matter hyperintensity burden as the strongest contributors to model predictions.

Conclusions: While predicting amyloid-β positivity using brain MRI and ML in asymptomatic stages is challenging, interpretable ML could provide insight into neuroimaging biomarkers of preclinical AD. Larger studies are needed to improve the model performance, particularly within the intermediate pTau217 levels.

POSTER # 65

SLEEP DISRUPTION FOLLOWING TRAUMATIC BRAIN INJURY GENERATES EARLY ALZHEIMER'S-RELATED PROTEIN VARIANT PATHOLOGY IN WILD-TYPE MICE. Schulz P, He P, Tsvechenko O, Mendez MV, Beauregard LL, Szewczak M, Mannino GS, Green TRF, Rowe RK, Sierks MR. Arizona State University; University of Colorado Boulder; Stanford University School of Medicine; Arizona Alzheimer's Consortium.

Background: Traumatic brain injury (TBI) is linked to an increased risk of Alzheimer's disease (AD) and related dementias (ADRDs) through neuronal stress and loss of proteostasis. TBI promotes generation of toxic amyloid-beta, tau, and TDP-43 variants associated with ADRDs and frequently disrupts sleep, potentially reducing glymphatic clearance of protein variants and metabolic waste products. We hypothesized that acute TBI stress combined with post-TBI sleep disruption (SD) would promote accumulation of ADRD-related protein variants in wild-type mice. We assessed regional protein-variant levels following TBI and SD and correlated variant levels with behavioral outcomes, including sex-dependent differences.

Methods: Adult male and female C57BL/6J mice were subjected to mild or moderate TBI using midline fluid percussion injury (mFPI) or a sham procedure. Following a 7-day recovery period, sleep was disrupted for 7 days using automated sleep-fragmentation cages. Sensorimotor function was evaluated using rotarod (RR) and modified neurological severity score (NSS), while cognitive and behavioral outcomes were assessed using novel object recognition and open-field testing. Brain tissue was collected at 15 days post-injury (DPI) and analyzed by immunohistochemistry using antibodies recognizing eight ADRD-related variants of amyloid-beta, tau, and TDP-43. These variants are present in ADRD brain tissue but absent from age-matched cognitively normal tissue. Regional variant levels were quantified using ImageJ and correlated with behavioral performance.

Results: TBI produced short-term sensorimotor and neurological deficits that largely resolved by 14 DPI, while all eight ADRD-related protein variants were detected across mice and brain regions. In mice without SD, two significant correlations linked increased variant levels with behavioral deficits, while 15 linked lower variant levels with deficits. SD did not independently impair behavior at 14 DPI but modified recovery in an injury- and sex-dependent manner and altered protein-variant patterns. In SD-exposed mice, 14 significant correlations linked increased variant levels with behavioral deficits, while 19 linked lower variant levels with deficits. F9T tau levels in the corticospinal tract correlated with rotarod, NSS, and open-field outcomes at 14 DPI in sleep-disrupted mice. C6T amyloid-beta showed both positive and negative relationships with behavioral deficits depending on brain region and behavioral measure. Marked sex-dependent differences were observed in behavior, protein-variant levels, and protein-behavior correlations, with females exhibiting higher levels of several amyloid-beta, tau, and TDP-43 variants.

Conclusions: TBI induces short-term behavioral deficits and the selective, region-specific generation of ADRD-related amyloid-beta, tau, and TDP-43 variants in wild-type mice. Post-TBI SD modified behavioral recovery and protein-variant patterns in an injury- and sex-dependent manner. Specific amyloid-beta, tau, and TDP-43 variants showed positive or negative correlations with behavioral outcomes depending on stress condition, brain region, behavioral measure, and sex. Females exhibited elevated levels of several key amyloid-beta and tau variants, suggesting increased susceptibility to ADRD-related pathology. These findings demonstrate that early ADRD-related protein pathology can be generated following TBI and modified by subsequent sleep disruption.

POSTER # 66

SEX-SPECIFIC MODULATION OF INNATE IMMUNE RESPONSES AND BLOOD–BRAIN BARRIER PERMEABILITY FOLLOWING EXPERIMENTAL TRAUMATIC BRAIN INJURY.
Simmons A, Chimene S, Herrera-Diaz D, Willingham C, Witten A, Bimonte-Nelson H, Plaisier C, Sirianni R, Stabenfeldt S. Arizona State University; University of Massachusetts Chan Medical School; Arizona Alzheimer's Consortium.

Background: Traumatic brain injury (TBI) results from an external blow or jolt to the head, causing primary and secondary injury sequalae. The primary injury phase consists of the injury-induced tissue damage and transitions to a chronic phase of secondary cellular cascades the involve dysfunction of the blood-brain barrier (BBB) and neuroinflammation. Previous studies have demonstrated robust innate immune responses to TBI, including the extravasation and activation of neutrophils, macrophages and dendritic cells at acute timepoints. Once at the injury site, innate immune cells interact with local signals and become activated, further promoting an inflammatory environment and contributing to BBB breakdown. Importantly, chronic neuroinflammation and increased BBB permeability can lead to the development of neurodegenerative disease. In other models of CNS injury, others have shown that reduction of innate immune responses leads to improved functional and pathological outcomes, yet the impact of augmenting the innate immune response in TBI has not been fully explored. Therefore, this study assessed the impact of acute administration of the anti-inflammatory drug, diclofenac, on innate immune cell infiltration into the brain and BBB permeability.

Methods: The well-established mouse controlled cortical impact (CCI) model was used to induce a unilateral moderate focal TBI over the primary somatosensory cortex in C57BL/6J mice (10-11wks old). Intraperitoneal injections of 40mg/kg diclofenac sodium or saline were given immediately after injury. Male and female cohorts were assessed; naïve cohorts served as baseline controls. Brain tissues collected 24 hrs post-treatment to evaluate microglia, neutrophil, dendritic cell (DC), and monocyte/macrophage markers via flow cytometry. BBB permeability at 24 hrs post-treatment was assessed using the Evans Blue Assay.

Results: At 24hrs post-TBI, our data support sex-dependent changes in injury-induced innate immune cell infiltration and BBB permeability after treatment with diclofenac. Only the female cohort showed a decrease in neutrophil infiltration after diclofenac treatment compared to the sex-matched saline vehicle. Notably, neutrophil infiltration for the female diclofenac cohort decreased to comparable levels as both saline and diclofenac injured male cohorts. In concert with female-specific innate immune alterations, we found that only the female cohort experienced a decrease in BBB permeability after treatment with diclofenac.

Conclusions: These findings underscore the importance for including sex as a biological variable in preclinical TBI research, particularly when evaluating the effects of immunomodulatory therapeutic interventions. Ultimately, this study links early immunomodulation to reduced BBB permeability in females, providing a critical insight into therapeutic strategies aimed at limiting secondary injury sequelae that contribute to neurodegeneration after TBI.

POSTER # 67

AGE-RELATED DIFFERENCES IN TRANSCRIPTIONAL VARIABILITY ARE BRAIN REGION- AND CELL TYPE- SPECIFIC. Smith EA, Watkins KL, Yang W, DeCasien AR, O'Neill MB, Bohlen M, Melin AD, Higham JP, Montague MJ, Platt ML, Shendure J, Chiou KL, Snyder-Mackler N. Arizona State University; University of Washington; Seattle Hub For Synthetic Biology; Computational And Evolutionary Neurogenomics Unit, NIA; Duke University; University of Calgary; New York University; New York Consortium in Evolutionary Primatology; University of Pennsylvania; Howard Hughes Medical Institute; Allen Discovery Center For Cell Lineage Tracing; University of Alabama at Birmingham; ASU-Banner Neurodegenerative Disease Research Center; Arizona Alzheimer's Consortium.

Background: Inter-individual differences in extrinsic factors, genetic background, and stochastic processes contribute to variation in aging, yet their molecular consequences across brain regions and cell types remain unclear. Regions and cells with age-associated inter-individual variability (IIV) differences may highlight biological processes underlying divergent aging trajectories, and those with stable IIV reflect conserved aging patterns.

Methods: We examined age-related transcriptional differences in free-ranging rhesus macaques, whose genetic similarity to humans and age range that can be sampled offer a valuable model to study aging mechanisms. We drew on snRNA sequencing of 5.3 million cells from 11 brain regions in 53 macaques (aged 3–21 years) to characterize age-related transcriptional IIV at single-cell resolution. We tested for age differences in IIV using: 1) cell composition, quantified by beta diversity; and 2) cell-type-specific transcription, quantified by gene expression variance at the transcriptome-wide or gene level.

Results: Age was associated with region- and cell type- specific differences in compositional and transcriptional diversity. Hippocampal GABAergic neurons showed higher compositional diversity in older individuals ($q=0.031$). Transcriptional variability was higher at older ages in some cell subtypes, such as dlPFC myelinating oligodendrocytes ($q=0.013$) and lower in others, such as EC homeostatic astrocytes ($q=0.024$). We characterized the impact of this variability through functional enrichment and cell-cell communication assays and identified putative upstream regulators through gene regulatory networks (GRNs). We found mitochondrial function, cell signaling, and GRN signatures unique to subtypes that show variability differences with age. Some subtypes showed variability and signaling differences with age, including stronger signaling to oligodendrocyte precursor cells ($q<1e-20$, Fold Enrichment (FE) = 6.2–28.4 in ACC, CN, IPP, M1, and dlPFC) and weaker signaling to oligodendrocytes ($q<1e-20$, FE=1.5–9.8 in CN, EC, HIP, IPP, M1, MB, NAc, dlPFC, and mdTN).

Conclusions: By pinpointing regions, cell types, and genes that are variable or stable with age in a human-relevant animal model, our work localizes regulatory mechanisms that explain how brains age differently.

POSTER # 68

GENERALIZABILITY OF DEEP LEARNING BRAIN AGE MODELS TO UNDERREPRESENTED POPULATIONS: COMPARING IMAGE-BASED AND FEATURE-BASED MODELS IN THE STRONG HEART STUDY. Sohankar J, Su C, Protas H, Luo J, Chen Y, Chen K, Ali T, O'Leary M, Umans J, Buchwald D, Manson S, Reiman EM, Suchy-Dicey A, Su Y. Banner Alzheimer's Institute; Arizona State University; University of Oklahoma Health Sciences; Missouri Breaks Industries Research; MedStar Health Research Institute; University of Washington; University of Colorado; Boston University; Arizona Alzheimer's Consortium.

Background: Age is a primary disease risk factor and a central focus of neuroimaging research. Brain age prediction models based on MRI scans have shown promise as biomarkers of aging and disease risk. However, most existing models are trained and evaluated on cohorts with limited demographic diversity, where the primary groups are White participants followed generally by Latino participants- raising concerns about generalizability to underrepresented populations such as American Indians.

Methods: We developed two deep learning models to predict brain age; one using MRI scans, and another one using SynthSeg-derived MRI features, termed as IMG-model and FE-model, respectively. The FE-model was trained on 2,713 participants from the National Alzheimer's Coordinating Center (NACC), and the IMG-model on 7,932 participants from five datasets that included those from NACC. Both models were trained on MRIs only from cognitively normal participants (using an 80/10/10 split) for 100 epochs. The optimal model was evaluated on the full NACC dataset of 5,460 unique participants (containing normal and impaired individuals), as well as an independent set of 703 American Indians participants in the Strong Heart Study (SHS). The results from the SHS cohort were used for the following statistical analysis. For both models, we performed linear regression analysis controlling for age, sex, and education to assess associations between the brain age gap (BAG) -defined as the difference between predicted and chronological age- and cognitive and clinical measures (including Clinical Dementia Rating Global Score (CDR), Modified Mini-Mental State Examination (3MSE), diabetes and hypertension status, as well as estimated glomerular filtration rate). Finally, we performed a T-test on the difference of BAG mean values between the two models.

Results: The FE-model and IMG-model respectively achieved a mean absolute error of 4.51 and 4.49 years on the NACC cohort and 4.48 and 5.37 years on the independent SHS testing dataset, demonstrating stable performance in case of FE-model across demographically distinct populations. In the FE-model and SHS cohort, larger BAG was significantly associated with lower 3MSE scores (Beta=-0.05; $p < 0.01$) and diabetes (Beta=1.07; $p < 0.01$), but not with glomerular filtration rate ($p=0.07$) or hypertension ($p=0.15$). For the IMG-model, larger BAG was significantly associated with even lower 3MSE scores (Beta=-0.07; $p < 0.01$) and larger diabetes (Beta=2.04; $p < 0.001$), but not with glomerular filtration rate ($p=0.1$) or hypertension ($p=0.56$), similar to FE-model. Finally, in the SHS cohort, for the FE-model the mean BAG was 0.62 years (slight over-estimation) and for IMG-model it was -1.87 years (under-estimation). The T-test yielded an extremely small p-value (~E-14), so the two models have different mean BAG, and the 95% CI of the two models mean BAG difference is [1.84, 3.13].

Conclusions: We present two generalizable brain age models and observe that the FE-model performs better in maintaining accuracy across cohorts and has lower standalone BAG. The observed associations between BAG and cognitive and clinical measures support its potential utility as a biomarker for cognitive decline and related health outcomes in heterogeneous populations.

POSTER # 69

AGING DECREASES COUPLING OF SPATIALLY TUNED MPFC-HC NEURONS IN SPATIAL DECISION MAKING. Srivathsa S, Sterzinar C, Sponseller M, Garza V, Church E, Warrier M, Cowen SL, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

Background: Spatial decision-making requires animals to integrate spatial context, recent experience and rewards to guide choices. Flexible decision-making is altered with age, but the underlying changes to hippocampal (HC) and medial-prefrontal cortical (mPFC) neurons that support spatial decision-making remain unclear. Neurons in the intermediate (iHC) and ventral (vHC) hippocampus regions project directly to prelimbic (PL) and infralimbic (IL) cortices of the mPFC, providing a pathway for interactions between these regions.

Methods: To examine how HC-mPFC activity change with age, we trained young (n=8) and old (n=8) male F344 rats on a spatial alternation task. Old rats showed less accurate performance on the spatial working memory component of the task compared to young, even after 21 training sessions. Following acquisition, rats were implanted with dual-bundle hyperdrives targeting CA1 and CA3 regions of the iHC and vHC, as well as PL and IL regions of the mPFC. Neural activity was recorded simultaneously from these regions for an additional 13 to 21 sessions, during which old rats continued to show spatial working-memory impairments.

Results: Consistent with dorsal HC, place cell peak firing rate, place field size, and spatial sparsity did not differ between age groups (Crown et al., 2022). Also similar to dHC, spatial information-per-spike was increased in the vHC of old rats. In the mPFC, spatially tuned neurons showed similar properties between age groups, except for lower peak firing rates in the IL region of aged rats. The fraction of spatially selective mPFC cells showing bidirectional firing was also lower in aged rats than in young. We observed significant pairwise correlations between ivHC and mPFC spatially tuned neurons in young and old rats on the spatial working memory component of the task. When pairwise correlations were examined pre- and post-choice, young rats showed increased HC-mPFC correlations pre-choice. Old rats did not show this effect.

Conclusions: If the higher ivHC-mPFC pre-choice correlation in the young rats facilitates decision-making, the lack of this correlation in old rats may contribute to their worse spatial working-memory performance.

POSTER # 70

DRAW-10: A WEEKLY BLOOD DRAW STUDY TO UNDERSTAND THE BIOLOGICAL FLUCTUATIONS OF PLASMA PTAU-217. Starner MK, Walsh T, Erickson C, Pandya S, Knox JC, Anguiano J, Dieckhoff K, Liu J, Denkinger MN, Reiman EM, Ashton NJ, Langbaum JB. Banner Alzheimer's Institute; Banner Sun Health Research Institute; Banner Alzheimer's Institute – Tucson; Arizona Alzheimer's Consortium.

Background: Blood biomarkers are becoming pivotal tools in the diagnosis and management of neurodegenerative diseases, such as Alzheimer's disease (AD). A leading blood biomarker for AD, pTau-217, demonstrates high sensitivity and specificity for identifying individuals who are likely to have AD pathology or are at risk for AD dementia. However, blood biomarker levels are subject to fluctuation by some co-morbidities and other factors not yet well understood (Brum et al, 2023). Characterizing these fluctuations is crucial given the increasing use of blood tests in making biomarker-supported AD diagnosis and as eligibility tests for clinical trial enrollment.

Methods: Draw-10 was an observational research study exploring fluctuations in blood biomarkers over a short period and investigating potential associated drivers of these fluctuations. Draw-10 enrolled participants aged 50-80 years in the Phoenix and Tucson metro areas with normal cognition or MCI based on a screening MoCA score of ≥18. Over 9 weeks, participants provided 10 plasma samples (fasting), completed questionnaires at each visit regarding their sleep, stress level, alcohol use, and exercise behaviors, and provided most recent medications. Samples were sent to the Michael T. Zuendel Family Biomarker Laboratory at Banner Sun Health Research Institute, where pTau-217 and Aβ42 were measured using the RUO cobas e801 (Roche Diagnostics) assay. Numerical and categorical results (negative, intermediate, positive) were provided. After sample analysis was completed, participants could opt into learning their consistent pTau-217 categorical result via a telehealth visit with a clinician.

Results: 100 participants (96 cognitively unimpaired, 4 MCI) were enrolled between January-June 2025, and 99 participants completed the study. Plasma samples from all 100 participants were analyzed. Analysis was randomized within each participant and performed blinded to any participant information. Results estimated the analytical and biological variation for pTau-217 assays, reference change values, frequency of major fluctuations in blood biomarkers, and if this can be attenuated by different assay immunoassay designs or ratios. Examining the data from participants who completed all 10 blood draws, 65% of participants (n=64) had negative results at each timepoint, 2% of participants (n=2) had positive results at each timepoint, and no participants had intermediate results at each timepoint. 33% of participants (n=33) crossed categories across the study. Of those, 64% of participants (n=21) crossed between negative and intermediate, 9% (n=3) between intermediate and positive, and 27% (n=9) between negative, intermediate, and positive. Additional analyses are underway to examine probable sources of fluctuations.

Conclusions: The Draw-10 study provides important data about the frequency in fluctuations between pTau-217 categorical cut-points. The data suggests the importance of repeat testing to aid clinical decision making and clinical trial enrollment based on pTau-217. The data highlights the need for further understanding of biological variation of AD blood biomarkers. This may improve biomarker-supported clinical decisions, prevent inaccurate participant screening decisions, and help determine the guidance for repeat pTau-217 testing to ensure reliable measurement.

POSTER # 71

EXPLORING THE MECHANISM OF ACTION OF THE ANTI-PRION COMPOUND CHICAGO SKY BLUE 6B. Stephens HR, Whetzel A, Lewis KN, Salehi Y, Yacktman B, Beans A, Haley NJ, Mercer RCC. Midwestern University; Arizona Alzheimer's Consortium.

Background: Prion diseases are invariably fatal protein misfolding neurodegenerative diseases of humans and other animals. To date, there are no available treatment options for these devastating disorders, making the identification and characterization of novel anti-prion compounds a high priority. The central event in these diseases is the structural conversion of the cellular prion protein (PrPC) into a disease-causing conformation (PrPSc), which replicates through a self-templated mechanism. The search for small molecule therapeutics that target PrPSc directly is complicated by the existence of prion strains; distinct structures of PrPSc imprinted upon molecules of PrPC with identical primary structure. Additional challenges are presented by variations in the post-translational proteolytic processing of PrPC by different cell types. Here, we investigate the mechanism of action of Chicago Sky Blue 6B, which has been reported to interact with PrPC within the vicinity of amino acids 91-119, blocking the binding of A-beta oligomers and inhibiting the propagation of PrPSc.

Methods: Immortalized cell culture, western blot, conformational stability assay, Real Time Quaking Induced Conversion (RT-QuIC) assay, scrapie cell assay.

Results: Our investigations were spurred by the observation that the anti-prion effects of Chicago Sky Blue 6B against RML prions were significantly different across cell types: EC50 using N2a cells = 3.8 uM, EC50 using CAD5 cells = 15.7 uM ($p=0.0006$). We investigated the molecular underpinnings of this observation by 1) assaying the anti-prion activity of CSB using multiple prion strains across several cell types, 2) probing differences in the proteolytic processing of PrPC by each cell type, and 3) examining the conformational stability, seeding activity, and infectivity of prions treated with Chicago Sky Blue 6B.

Conclusions: The use of a wide array of assays to examine distinct aspects of prion biology is critical for a complete understanding of the mechanism of action of candidate therapeutic molecules.

POSTER # 72

A HUMAN TELOMERE PROTECTION PROTEIN THAT MODULATES GAMMA-SECRETASE ACTIVITY INTERACTS WITH THE AMYLOID PRECURSOR PROTEIN. Swanson MJ, Sas A, Moon J, Godziela MG, Doughty MF, Whetzel A, Lewis KN, Bae NS. Midwestern University; Arizona Alzheimer's Consortium.

Background: The accumulation of amyloid beta (Abeta) peptides that form plaques in the human brain is a hallmark of Alzheimer's disease (AD), a brain disorder resulting in progressive cognitive impairment and memory loss. The Abeta peptides are produced by the successive cleavage of the amyloid precursor protein (APP) by beta-secretase and gamma-secretase. APP is a protein that spans the plasma membrane. Beta-secretase cleaves APP in its extracellular domain. The remaining fragment is cleaved in the transmembrane domain by gamma-secretase, which releases Abeta peptides into the extracellular space while the APP intracellular domain, or AICD, is released into the cell to enter the nucleus and affect gene expression. Gamma-secretase produces Abeta peptides mostly as the soluble Abeta40 with fewer insoluble Abeta42 peptides. Early-onset AD (EOAD) occurs in individuals under 60 years of age, and some cases are due to mutations in the genes encoding APP or the presenilins (PS1 and PS2) that are the catalytic subunits of the gamma-secretase complex. APP is not the only protein targeted by gamma-secretase. At least 148 other known proteins can be cleaved by gamma-secretase. How gamma-secretase activity is regulated, especially regarding specificity of targets for cleavage, is not well understood. However, the answer may be through naturally occurring proteins that modify gamma-secretase activity, or the gamma-secretase modulatory proteins (GSMPs). Four GSMPs were identified through interactions with gamma-secretase. The GSMPs were shown to modify the activity of gamma-secretase cleavage of APP or Notch, another gamma-secretase target. The mechanism(s) by which GSMPs regulate gamma-secretase activity on specific targets is unknown. The goal of this research is to determine the mechanism of how a novel GSMP identified in our lab can modify gamma-secretase activity.

Methods: Gamma-secretase activity was monitored using a genetic model we developed in the yeast Saccharomyces cerevisiae. Interactions among the proteins were performed using affinity (His6-, GST- and MBP-) tagged fusion proteins expressed in E. coli cells. Cell lysates were mixed, and proteins were purified on appropriate resins to bind the affinity tags. Eluted proteins were subjected to polyacrylamide gel electrophoresis and immunoblotting using antibodies to the affinity tags.

Results: In this study, we showed that the telomere protection protein RAP1 (TERF2IP) interacted in vitro with the hydrophilic, cytoplasmic amino terminus of PS1 (amino acids 1-85). RAP1 increased gamma-secretase activity in the yeast genetic model system. RAP1 interacted with the AICD, the intracellular domain of APP, but we did not detect a direct interaction between the amino-terminus of PS1 and the AICD.

Conclusions: Our results indicate that RAP1 is a GSMP. RAP1 regulates gamma-secretase activity by binding the target protein APP through its cytoplasmic domain (AICD). Once bound, RAP1 can bring APP to gamma-secretase for cleavage through RAP1's interaction with PS1. Though other work showed that APP interacted with PS1, those experiments used immunoprecipitations from cell extracts, so bridging proteins were likely to be present. Our continued studies will determine if the other GSMPs behave in a similar manner. In addition, we are determining the importance of the amino terminus of PS1 for activity and as a docking site for GSMPs.

POSTER # 73

CLINICAL IMPLEMENTATION OF P-TAU217 BLOOD BIOMARKER TESTING IN A PRIMARY CARE SETTING TO IMPROVE EARLY DIAGNOSIS AND ACCESS TO AMYLOID TARGETING TREATMENTS FOR ALZHEIMER'S DISEASE. Traslavina Jimenez J, Soltani L, Singh P, Siu H, Edmonds EC, Ashish D, Menchola M, Rapcsak SZ. Banner Alzheimer's Institute – Tucson; El Rio Health Care; University of Arizona; Midwestern University; Arizona Alzheimer's Consortium.

Background: Many patients with mild cognitive impairment (MCI) or early dementia due to Alzheimer's disease (AD) remain undiagnosed in primary care settings, preventing eligible individuals from receiving amyloid targeting treatments (ATT). To address this urgent clinical challenge, Banner Alzheimer's Institute-Tucson (BAI-T) partnered with El Rio Health to integrate p-tau217 blood biomarker testing into the clinical evaluation of patients presenting with memory complaints in order to improve early AD diagnosis and timely access to ATT.

Methods: We implemented an AD screening protocol for individuals 55 years and older presenting with memory complaints to El Rio primary care clinics that included p-tau217 testing and brief cognitive assessment (MMSE). Individuals positive for p-tau217 with an MMSE score of 20 or higher were referred to BAI-T for further evaluation for ATT. We also conducted didactic sessions for El Rio primary care providers addressing the role of p-tau217 in early AD diagnosis and appropriate use recommendations for ATT.

Results: Prior to implementation, no p-tau217 tests were ordered within El Rio primary care clinics. Since the start of our project, 246 tests have been ordered and of those completed, 53% were positive for AD pathology. The biomarker positivity rate for AD in El Rio clinics represents a significant improvement over clinical detection rates for early stage AD in primary care settings. To date, 26 El Rio patients have been evaluated at BAI-T to determine eligibility for ATT, 4 have qualified, 2 declined, and 10 are completing the required workup. Nine patients were found ineligible due to MRI exclusion criteria, medical comorbidities, or advanced dementia. BAI-T wait times for El Rio referrals were reduced to 2 months compared to the community standard of 3-12 months.

Conclusions: Our project significantly increased AD diagnostic accuracy in a primary care setting by incorporating p-tau217 testing into the initial evaluation of patients with memory complaints and established an expedited referral pathway between El Rio Health and BAI-T for access to ATT. Our partnership represents an important step toward reducing disparities in access to improved AD diagnosis and treatment in underserved Hispanic populations and provides a new model of AD care in the Tucson community.

POSTER # 74

PERSONALITY AND NEUROPSYCHOLOGICAL MEASURES WITH AND WITHOUT MIGRAINE IN A LONGITUDINAL COHORT OF COGNITIVELY NORMAL INDIVIDUALS STRATIFIED BY APOLIPOPROTEIN E GENOTYPE. Vanood A, Starling A, Woodruff BK. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Apolipoprotein E (ApoE) is involved in the pathogenesis of Alzheimer's disease, with the E4 allele conferring a faster progression of cognitive symptoms. There are few studies investigating the role of ApoE in migraine, although patients with migraine also experience cognitive symptoms. The purpose of this study was to determine if there were objective differences in personality and neuropsychological measures, as well as distribution of ApoE genotype, in patients with and without migraine.

Methods: Data was extracted from a longitudinal database of 1162 cognitively normal individuals. Data was analyzed at baseline (initial Epoch) and longitudinally (across all Epochs). Personality measures included NEO Personality Inventory (T-scores), the Personality Assessment Inventory (PAI, T-scores), the Hamilton Depression Rating Scale (HDRS), and Beck Depression Inventory (BDI). Cognitive performance was measured using raw scores for the Auditory Verbal Learning Task (AVLT), Controlled Oral Word Association Test (COWAT), Wechsler Adult Intelligence Scale (WAIS), Iowa Gambling Test (IGT), Judgement of Line Orientation (JOL) and Paced Auditory Serial Addition Test (PASAT). These personality and cognitive domains were compared between patients with a documented history of migraine and those without. ApoE4 allele carrier status was also compared.

Results: 86 patients had migraine. E4 carrier status was similar ($p = 0.17$), although there was a greater proportion of E4 homozygotes with migraine (22% vs 11%, $p = 0.015$). Individuals with migraine scored higher on the PAI Somatic Complaints subscale (52 vs 47, $p < 0.001$) and HDRS (3.41 vs 2.44, $p=0.025$). While patients with migraine had higher scores on AVLT long-term memory (LTM) (10.01 vs 9.33, $p=0.041$) and total learning (50.55 vs 48.31, $p=0.0270$), this was not significant (FDR >0.05). The remaining cognitive measures were comparable between groups. Among patients with migraine, E4 carrier status was not associated with differences in cognitive performance or personality traits.

Conclusions: Patients with migraine were more likely to score higher on the PAI Somatic Complaints subscale and HDRS. While neither cohort scored within the pathological range for these subscales, our findings suggest that individuals with migraine experience a greater proportion of non-migraine symptoms that may not otherwise be fully accounted for, or addressed, during neurology clinical encounters. Cognitive performance was comparable between groups.

POSTER # 75

TRENDS IN EPISODIC MEMORY AND COGNITIVE SYMPTOMS IN COGNITIVELY NORMAL APOE2 HOMOZYGOTES. Vanood A, Wicklund MR, Locke D, Langlais B, Caselli R, Woodruff BK. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Apoliprotein E (APOE) is a glycoprotein involved in varying risk of Alzheimer's Disease (AD). Specifically, the APOE4 allele confers an increased risk of AD while APOE2 is thought to be protective. The E2 genotype is rare and studies evaluating cognitive profiles and symptom burden for these individuals are sparse. We seek to determine if there are objective differences in neuropsychological performance, measured through the Auditory Verbal Learning Test (AVLT), as well as in subjective cognitive symptoms, measured through Multidimensional Assessment of Neurodegenerative Symptoms (MANS) scores, between individuals with the E2/E2 genotype compared to other genotypes.

Methods: Individuals in the Arizona APOE Cognitive Aging Cohort were assessed using baseline MANS-Self, MANS-Informant, and AVLT total learning and long-delay free recall. MANS scores >0 were considered "positive" for endorsed impairment. Unadjusted t-tests were used to compare age and cognitive measures between groups. Analysis of covariance was used for age-adjusted comparisons. MANS-Self and MANS-Impairment raw scores were compared (patient vs informant) within groups using paired t-tests. E2/E2 was compared pairwise to the other individual genotypes, as well as compared to the combined group of genotypes (non-E2/E2).

Results: A total of 1141 individuals were assessed, of which n=26 were E2/E2, n=120 E2/E3, and n=57 E2/E4. E2/E2 individuals were older than the combined non-E2/E2 group (70.0 years vs 58.8 years, $p< 0.05$), and age-adjusted long-delay free recall was lower compared to E2/E4, E3/E3, and E2/E3 groups (7 words vs 10 words vs 10 vs 10 words, each p0, there was no significant difference in average MANS-Self scores between E2/E2 and non-E2/E2 cohorts ($p=0.5991$). However, among informants reporting MANS-Informant scores >0, E2/E2 informant scores were significantly lower on average compared to non-E2/E2 informant scores ($p=0.0406$), although this did not persist after adjusting for age ($p=0.0843$).

Conclusions: APOE2 homozygotes demonstrated subtly lower, but age-normative, baseline episodic memory performance compared to other APOE genotypes. However, E2/E2 had comparable MANS-Self scores to other genotypes. This suggests that the lower cognitive performance of E2 homozygotes is not a product of selection bias in individuals endorsing subjective cognitive impairment. Validation of these findings in an additional large cohort of patients is underway.

POSTER # 76

ROPE-PULLING SYSTEM TO STUDY SENSORIMOTOR INTEGRATION BETWEEN UPPER-EXTREMITY KINEMATICS AND DISTANCE ESTIMATION IN AGING AND CLINICAL POPULATIONS. Vishwanath A, Farley B, Sherman S, Barnes C, Cowen S, Ekstrom A. University of Arizona, Parkinson's Wellness Recover Gym; Arizona Alzheimer's Consortium.

Background: Everyday tasks, such as picking up a coffee cup or tying shoelaces, requires coordinated upper-limb reaching, grasping and pulling movements. These tasks demand effective integration of sensory information, such as vision and proprioception, with motor commands and execution. Deterioration in sensorimotor integration ability, either during healthy aging or with cognitive/motor disorders, can increase inaccuracies in motor judgements that can adversely affect the quality of life in these individuals. Currently, there are limited bimanual and functional goal-directed tasks, which target upper-extremity movements that are sensitive and robust enough to characterize sensorimotor integration and inter-limb coordination in gross and fine motor movements. Therefore, there is a need for novel tasks, which target the understudied bimanual and non-gait related behaviors and can measure sensorimotor integration across diverse populations, such as in aging, neurodegenerative disease (Alzheimer's and Parkinson's disease), and walking-impaired populations. Thus, we have adapted an established string-pulling task from animal models as a translational rope-pulling system/task. Furthermore, we developed a variant of this task to assess the capacity of subjects to estimate and reproduce distances (lengths of rope) pulled given evidence that distance estimation is disrupted in aging, Alzheimer's disease, and Parkinson's disease.

Methods: The rope-pulling task allows for tracking upper-limb bimanual motor function and coordination (i.e., alternating reach, grasp, and pull movements) using a "continuous loop" of rope. We used machine vision (DeepLabCut) to measure precise sub-second kinematics of hand movement such as inter-limb coordination (phase and timing relationships), gross motor (reaching and pulling, overall movement speed/amplitude), and fine motor (grasping) movements during rope pulling. For evaluating distance reproduction, participants, in a given trial, remember a target distance of rope and reproduce the distance from memory. In addition, all participants will undergo standardized neuropsychological and motor assessments.

Results: This study aims to assess sensorimotor integration and detect changes in motor kinematics during distance estimation on the rope-pulling task. The relationship between motor kinematics and distance estimation will be assessed using a computational model to predict how distance perception alters motor control. We predict that the variability in inter-limb coordination will correlate most significantly with distance errors.

Conclusions: The rope-pulling task is well suited to assess sensorimotor integration specifically in upper-extremity movements. Additionally, the task is novel in its capacity to seamlessly incorporate cognitive goal-directed behaviors with complex functional movements.

POSTER # 77

DRAW-10: ASSESSING THE IMPACT OF LEARNING PLASMA PTAU-217. Walsh T, Erickson C, Starner MK, Knox JC, Pandya S, Langlois C, Dieckof K, Li J, Denkinger MN, Reiman EM, Ashton NJ, Langbaum JB. Banner Alzheimer's Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Blood biomarkers, such as plasma pTau-217, are becoming pivotal tools in the diagnosis and management of neurodegenerative diseases, such as Alzheimer's disease (AD). The growing use of blood tests, the shortage of dementia specialists, and, in the United States, the 21st Century Cures Act, which requires the immediate return of medical test results, heighten the need to identify ways to return results that are safe and comprehensible and minimize healthcare system burden.

Methods: The Draw-10 study explored fluctuations in blood biomarkers over a short period and characterized the impact of learning pTau-217 results. Participants aged 50-80 with normal cognition or MCI (based on a screening MoCA of ≥18) were eligible. Over 9 weeks, participants provided 10 plasma samples. Participants had the option to learn their consistent pTau-217 result via a telehealth visit with a clinician. Participants were sent educational materials about pTau-217 test results to review at their own pace. Participants choosing to learn their results were sent online surveys pre- and post-disclosure about their psychological well-being and satisfaction with and understanding of the information presented. Pre-disclosure surveys assessed anxiety and distress but did not affect eligibility to learn results. We requested post-disclosure surveys be completed approximately 1-7 days post-disclosure, though participants could complete the post-disclosure assessments at any point before study end. The post-disclosure survey assessed depression (PHQ-9), anxiety (PROMIS), distress, satisfaction with disclosure services, understanding of results, and information on who the participant shared their results with.

Results: 99 participants completed the Draw-10 study and 95 participants opted to learn their pTau-217 results. Participants were provided with a categorical result: negative (n=78, 79%), intermediate (n=18, 18%) or positive (n=3, 3%). Post-disclosure, average PHQ-9 scores were 2.19 (SD=3.12) and average PROMIS scores were 10.60 (SD=4.96). Four participants had PHQ-9 scores above the clinical threshold (≥10). Eight participants had PROMIS scores above the clinical threshold (≥20). Study clinicians reviewed scores above clinical thresholds and decided whether to follow-up with participants. Overall, participants were satisfied with the disclosure visit (n=91, 96%) and found the information useful (n=89, 94%). Participants most often shared their result with their spouse/significant other (n=64, 67%).

Conclusions: The Draw-10 study offers novel data about the tolerability of returning pTau-217 results. Overall, returning results via telehealth was well tolerated. These findings are consistent with the larger API eSMARTER study which demonstrated return of pTau-217 in a national sample did not result in psychological harm. The majority of Draw-10 participants were in the negative pTau-217 range so it will be necessary to gather additional data on how this information is tolerated for participants in the intermediate or positive range.

POSTER # 78

T CELL-BASED RECOGNITION OF NON-ABETA AMYLOID PRECURSOR PROTEIN (APP) PEPTIDE EPITOPE AND PROTEIN IN BLOOD AS POTENTIAL PRE-AMYLOID BIOMARKERS FOR ALZHEIMER'S AND RELATED MILD COGNITIVE IMPAIRMENT (MCI).

Wheeler CJ, Rissman RA, Sagare A, Barlow J, Watanabe J, Bourgoin P, Van Dam D, Vermeiren Y, De Reu H, De Deyn PP, Reed M, Busnel JM. T-NeuroDx; Ortega NeuroRx; NovAccess Global And StemVax LLC; Society For Brain Mapping & Therapeutics, World Brain Mapping Foundation; University of California, Santa Cruz; University of Southern California; Beckman-Coulter Life Sciences; University of Antwerp; University of Groningen and University Medical Center Groningen.

Background: Biomarkers for Alzheimer's disease (AD) are primarily based on amyloid beta, phosphorylated tau species and markers of neurodegenerative, which do not fully capture early disease induction or trajectory. We recently developed a CD8 T cell-induced mouse model that allowed development of a potentially pre-amyloid biomarker for AD that is based on quantification of age-related Amyloid Precursor Protein [APP] peptide-binding CD8 T ("hiT") cells in blood (PMID: 38995966) using an APP471-479/Human Leukocyte Antigen(HLA)-A2 multimer (pHLA) and flow cytometry. Levels of hiT cells distinguished AD and related MCI from normal aging controls with high accuracy, but only HLA-A2-positive patients are testable with the APP-specific reagent, limiting its utility to ~50% of patients expressing HLA-A2.

Methods: Binding to a non-self (ALIAPVHAV/HLA-A2) multimer was also observed by hiT cells in blood of HLA-A2-positive and HLA-A2-negative patients. We assessed binding and disease correspondence to this non-self pHLA by CD8 T cells from blood of HLA-A2-positive (n = 79) and -negative (n = 44) AD and MCI subjects, examined reproducibility of pHLA signal within normal blood specimens, and used a whole-blood antigen-induced reactivity (AIM) assay to examine T cell reactivity to APP protein in normal patients to expand assay format options independent of HLA-A2 restriction.

Results: In receiver-operating characteristic (ROC) analysis, the non-self pHLA binding in the HLA-A2-negative cohort revealed area under the curve (AUC) of 0.878 for AD and 0.816 for AD-related MCI ($P < 0.00001$, >78% sensitivity, >99% specificity), with disease tracking improved in the HLA-A2-positive cohort (AUC 0.912 for AD; 0.921 for AD-related MCI). We demonstrated signal reproducibility among cognitively normal cohorts from 4 distinct repositories and sample types (fresh and frozen whole blood, fresh PBMC, frozen buffy coats), provided CD8+ cells were present at physiological levels (minimally >2.5% and typically 5-40% of gated lymphocytes). Finally, we found significant CD4 and CD8 T cell reactivity to APP protein by AIM assay in normal patients.

Conclusions: Decreased pHLA multimer binding by CD8 T cells strongly corresponds to AD and MCI-AD in individuals, with one reagent being useful independent of HLA-A2 status, with signal levels reproducible in blood from distinct sources and handling conditions. Broader subpopulations of APP-reactive T cells were also detectable by AIM assay in normal patients. Together, this provides a working basis for expanding the utility of a potentially pre-amyloid blood biomarker for AD to all patients.

POSTER # 79

RAP1 DIRECTLY INCREASES γ-SECRETASE ACTIVITY INDEPENDENTLY OF ITS TELOMERIC FUNCTIONS. Whetzel A, Bae NS, Tauriainen M, Lewis KN, Swanson MJ. Midwestern University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is an age-related disorder that results in progressive cognitive impairment and memory loss, in part due to the deposition of amyloid β (Aβ) peptides in senile plaques. The sequential proteolytic cleavage of the amyloid precursor protein (APP) by β-secretase, followed by γ-secretase, produces the soluble Aβ40 with fewer insoluble Aβ42 peptides. Early-onset AD (EOAD), which occurs in individuals under 60 years of age, can be caused by mutations in the genes encoding APP or the presenilins (PS1 and PS2), the catalytic subunits of γ-secretase. The mutations in these genes lead to an overall increase in Aβ production and/or a shift in the peptide ratio toward Aβ42.

RAP1(TERF2IP) is a telomeric protein that maintains genome stability by preventing chromosome ends from degradation and illegitimate fusion. RAP1 is unable to associate with telomeres on its own, and it must be recruited by TERF2, a DNA-binding protein, to perform its function. RAP1 has also been shown to affect gene expression by associating with TERF2 at extratelomeric sites. Our data showed that RAP1 interacts with the PS1 subunit of γ-secretase and that, when RAP1 was overexpressed in human U251 glioblastoma cells, Aβ peptide levels increased. The goal of this research is to determine whether the effect of RAP1 on Aβ peptide production is due to a direct effect on γ-secretase activity or due to its roles in the nucleus protecting telomeres and altering gene expression.

Methods: Two independent mutations in human RAP1 were created: Ile312Arg and Phe336Arg. Each of the Ile312Arg and Phe336Arg amino acid substitutions in RAP1 abrogates its interaction with TERF2. RAP1 wild-type and mutant alleles were cloned into a human expression vector under the CMV promoter fused to the FLAG epitope tag. The RAP1 alleles were transiently transfected into human U251 glioblastoma cells. RAP1 levels were measured via immunoblotting, and RAP1 localization was determined by cellular fractionation and immunoblotting. Aβ peptides levels in the media were measured using enzyme-linked immunosorbent assays (ELISAs).

Results: In this study, we show that overexpressed RAP1 and RAP1 mutant constructs lead to accumulation of the protein in the cytoplasm, whereas nuclear levels remain constant. We show that overexpression of the RAP1 wild-type protein increases Aβ peptides, and that overexpression of the RAP1 mutants also increases Aβ peptides, similarly to the wild-type protein.

Conclusions: Our data indicate that RAP1 plays a direct role in regulating γ-secretase activity, independent of TERF2's functions at telomeres and in gene expression.

POSTER # 80

BRAIN CHOLINE DEFICIENCY IN PRIMARY TAUOPATHIES AND THERAPEUTIC BENEFITS OF CHOLINE SUPPLEMENTATION IN THE PS19 MOUSE MODEL OF TAUOPATHY. Winslow W, Martin A, Judd JM, Turk J, Bartholomew SK, Serrano GE, Beach TG, Velazquez Jr. R. Arizona State University; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: The role of environmental and dietary factors in tauopathies remains poorly understood. Primary tauopathies are neurodegenerative disorders characterized by tau pathology, including Progressive Supranuclear Palsy (PSP), Corticobasal Degeneration (CBD), Pick's disease, and Frontotemporal Dementia (FTD). In contrast, secondary tauopathies, such as Alzheimer's disease (AD), arise when tau abnormalities develop secondary to another disease process. Although some cases are genetic, most are sporadic, suggesting that modifiable environmental factors contribute to disease risk and progression. Homocysteine (Hcy), a diet-sensitive amino acid elevated in tauopathies, promotes tau pathology through activation of tau kinases. Choline lowers Hcy levels and supports membrane phospholipid synthesis, epigenetic regulation, and acetylcholine production. Importantly, most adults fail to meet recommended choline intake levels, making choline insufficiency a common and potentially modifiable risk factor. Choline deficiency has been linked to increased inflammation, amyloid-beta accumulation, and tau pathology, whereas supplementation has demonstrated neuroprotective effects. However, brain choline status in primary tauopathies and the impact of altered choline intake on tau-driven disease progression remain unknown.

Methods: We quantified choline levels in postmortem superior frontal gyrus tissue, a region vulnerable to primary tauopathies, from individuals with PSP, CBD, and Pick's disease and age-matched controls (n = 4–8/group). We further examined the effects of dietary choline in PS19 (P301S tau) and wild-type mice maintained on choline-deficient (0.5 g/kg), adequate (1.1 g/kg), or supplemented (5.0 g/kg) diets from 3–9 months of age. Spatial cognition was assessed using the Barnes maze, and circulating choline, hippocampal tau phosphorylation (T181 and S396), and plasma biomarkers of astroglial activation (GFAP) and axonal injury (NfL) were measured.

Results: Primary tauopathy cases exhibited significantly lower brain choline levels than controls. In mice, circulating choline reflected dietary intake. Choline deficiency exacerbated hippocampal tau hyperphosphorylation, increased plasma GFAP and NfL, and worsened disease-related outcomes in PS19 mice. In contrast, choline supplementation partially rescued spatial cognition, reduced tau hyperphosphorylation, and lowered GFAP and NfL levels. These bidirectional effects were particularly pronounced in females.

Conclusions: Collectively, these findings identify reduced brain choline as a feature of primary tauopathies and demonstrate that dietary choline supplementation mitigates pathological and cognitive deficits in a tauopathy model. Given the central role of tau pathology across primary tauopathies and AD, these results support further investigation of choline as a safe, accessible, and modifiable therapeutic strategy for tau-mediated neurodegenerative disease.

POSTER # 81

STATE-DEPENDENT NETWORK DEDIFFERENTIATION IN THE AGING BRAIN. Yu Y, Raffaelli Q, Grilli MD, Andrews-Hanna JR. University of Arizona; University of Calgary; Arizona Alzheimer's Consortium.

Background: Network dedifferentiation—increased cross-talk between large-scale functional networks—is a hallmark of aging that is consistently linked to age-related changes in memory and executive function. Traditionally, this phenomenon has been studied using static connectivity metrics. However, extensive evidence demonstrates that global network coupling are highly dynamic, modulated by task demands and moment-to-moment cognitive contexts. It remains unclear whether age-related dedifferentiation is a uniform breakdown or if it fluctuates across intrinsic brain states, and whether aging impairs network flexibility. We investigated the temporal dynamics of global network coupling to determine how dedifferentiation manifests within behaviorally relevant, transient brain states.

Methods: During fMRI, participants underwent one rest and two think-aloud runs continuously verbalizing unprompted thoughts. Each run lasted 7 minutes. Final analyses include 21 young adults (20-35 yrs) and 25 older adults (60-85 yrs) after excluding participants with excess movement in the scanner.
Thought verbalizations were continuously coded along an internal-external content. To identify recurring, transient brain states, we fitted a Hidden Markov Model (HMM) to BOLD time series across 17 cortical networks to segment the data into discrete, recurring brain states. Network modularity was calculated globally and within each state. Linear mixed-effect models assessed how age and brain state interact to affect modularity. Network flexibility was quantified as an individual's maximum minus minimum modularity across visited states.

Results: The HMM identified states linked to moment-to-moment thought (Yu et al., 2025): S5 (default mode network) tracked early internal thought, S2 (executive control/dorsal attention networks) tracked external thought, and S7 (medial temporal lobe/DAN) engaged during later internal elaboration. Older adults exhibited significantly lower average modularity than young adults (0.119 vs. 0.147, $p < .001$). Modularity varied significantly across states for both groups—highest in S7 and lowest in S1 (a "passive state" not directly associated with generating either internally or externally oriented thoughts). State-dependent modularity indicates that the spontaneous unfolding of varied thought content is associated with ordered reconfiguration of brain network coupling. A significant age-by-state interaction revealed that age-related modularity differences fluctuate by state. Notably, older adults showed a significantly smaller range of modularity variability ($t = -5.01$, $p < .001$), suggesting reduced functional network flexibility.

Conclusions: Our findings indicate that age-related network dedifferentiation is dynamic and state-dependent rather than a uniform global breakdown. Older adults demonstrate restricted network flexibility, evidenced by a constrained range of modularity fluctuations as they transition across changing cognitive states. The suggests that age-related changes may link to a loss of transient network adaptability to meet moment-to-moment shifting cognitive demand. Temporal network dynamics thus add new insight into aging vulnerabilities beyond static metrics.

POSTER # 82

DATA-DRIVEN COGNITIVE CLUSTERS IN A NON-DEMENTED VASCULAR-ENRICHED POPULATION. Zahra S, Edmonds EC, French SR, Wiskoski HE, Arias JC, Waughman X, Orobiyi E, Vidana P, Escareno CE, Ally M, Johnson K, Mushtaq R, Alexander GE, Rapcsak SZ, Weinkauf CC. University of Arizona; Banner Alzheimer's Institute – Tucson; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Cerebrovascular disease and vascular risk factors have important contributions to cognitive impairment either directly or by promoting the development of Alzheimer's disease (AD) neuropathology. The aim of this work was to use a data-driven approach to identify unique cognitive groups in a non-demented vascular population and examine the association between neuropsychological profiles, AD biomarkers, and measures of vascular disease.

Methods: The first 219 participants enrolled in our prospective Carotid and Minds (CAM) study (participants aged 50-85 with ≥2 vascular comorbidities with or without asymptomatic carotid stenosis) were included. Participants underwent a full UDS neurocognitive battery assessing multiple cognitive domains (memory (M), language (L), processing speed (PS), executive function (EF), and visuospatial (VS). Dementia, stroke in the previous 6 months, and other neurological disorders were exclusionary. Hierarchical cluster analysis was performed for age, sex, and education-adjusted cognitive domain z-scores. Measures of vascular disease and plasma pTau217 levels were compared among the resulting cognitive groups.

Results: Participants had a mean age of 72±7 years, with 57% males, and a mean education of 14.5±2.9 years. Five cognitive clusters were identified. High-All domains (16.4%, All $z>0$), Normal-All domains (36.5%, All $z\approx0$), Normal-Low VS (21%, VS z=-0.42), Non-Amnestic (16.8%, M z=-0.36, PS z=-1.43, EF z=-1.30), and Amnestic (9%, M z=-1.44, PS z=0.31, EF z=-0.08) clusters. Vascular risk factor (hypertension, diabetes, smoking, and hyperlipidemia) prevalence was similar across 5 clusters. However, the non-amnestic cluster with very low PS and EF had the highest carotid stenosis severity (65% vs 49-57%), although not statistically significant. This group also had the highest mean log pTau217 levels (-0.39±0.63, p= 0.03). The amnestic group had less severe carotid stenosis (49%) and lower pTau217 level (-0.62±0.57).

Conclusions: Our data-driven approach identified both amnestic and non-amnestic cognitive profiles within a vascular disease cohort. Association of AD pathology (pTau217) with a non-amnestic group contrasts with the memory domain impairments that characterize classic AD presentation. Our findings suggest that both vascular and neurodegenerative pathways may contribute to tau hyperphosphorylation resulting in distinct profiles of cognitive impairment. Further assessment of these pathways associated with AD pathology could help in understanding vascular contributions to cognitive impairment and dementia.

POSTER # 83

HYPERTENSION IS ASSOCIATED WITH BETTER BRAIN HEALTH OUTCOMES IN OLDER-AGE ASYMPTOMATIC CAROTID DISEASE POPULATIONS – A MULTI-COHORT STUDY.

Zahra S, Hong AT, Arias JC, French SR, Wiskoski HE, Luu IY, Oxnam EB, Orobiyi EO, Ally M, Escareno CE, Culwell G, Heitkamp E, Vasquez F, Vidana P, Waughman X, Hillis M, Johnson K, Jordan JD, Hishaw GA, Bedrick EJ, Vitali F, Mushtaq R, Altbach M, Pruzin JJ, Huges T, Alexander GE, Tan TW, Weinkauf CC. University of Arizona; University of Southern California; Barrow Neurological Institute; Banner University Medical Center – Phoenix; Wake Forest University; Arizona Alzheimer's Consortium.

Background: Blood pressure (BP) management is highly relevant for cardiovascular and brain health outcomes. Although clinical guidelines are trending towards increasingly strict BP control, some discordant results evaluating dementia-related outcomes indicate that more research is needed. Asymptomatic extracranial carotid atherosclerotic disease (aECAD), a hallmark cerebrovascular disease affecting >10% of those over the age of 60, may represent a key subpopulation unaccounted for in previous studies.

Methods: Using our Carotids and Minds prospective study and TriNetX, a nationwide medical record database, we evaluated the association of hypertension status with dementia-related outcomes in adults ≥50 years of age with and without aECAD. We investigated secondary effects of age, systolic BP (SBP) ranges, hypertension medications, cardiovascular outcomes, and treatment of aECAD with carotid endarterectomy (CEA).

Results: After controlling for relevant confounders, we found that hypertension was significantly associated with protective effects for cognition(β=0.47, $p< .01$), pTau217(β= -0.52, $p< .01$), Alzheimer's disease(HR=0.56[0.52-0.61]), non-AD dementia(HR=0.66[0.63-0.68]), and MCI (HR=0.69[0.64-0.74]), with strongest risk reduction in aECAD patients >81 years of age. CEA mitigated these protective associations (HR=0.85[0.54-1.34]), and opposite associations of hypertension were seen in patients without aECAD. Still more, a SBP range of 140-159 mmHg optimized protective effects with no significant increase in major cardiovascular events and death.

Conclusions: In summary, hypertension appears protective in patients with aECAD for dementia-related outcomes, promoting the need for future clinical trials focusing on individualized BP goals and addressing cerebrovascular disease. More broadly, these data further highlight cerebrovascular disease as relevant in brain health and aging.

POSTER # 84

RE-ALIGNMENT OF WGS DATA AND META-ANALYSIS OF MULTIPLE TRAITS IDENTIFIED NOVEL GENETIC RISK LOCI ON THE X CHROMOSOME FOR ALZHEIMER'S DISEASE.
Zhang X, Rastogi A, Hanus S, Dharmendra Mohan Prabu HV, Trivedi MR, Shah J, Chen Y, Readhead BP, Wu T, Su Y, Reiman EM, Wilson MA, Wang Q. Arizona State University; Banner Alzheimer's Institute; Center for Genomics And Data Science Research, National Human Genome Research Institute, National Institutes of Health; Arizona Alzheimer's Consortium.

Background: The X chromosome remains understudied in its contributions to Alzheimer's Disease (AD), due to technical challenges in processing and analyzing genotyping data especially next generation sequencing data on the sex chromosomes.

Methods: We adopted a sex chromosome complement (SCC)-informed whole-genome sequencing (WGS) data analysis workflow, which consists of proper masking of the Y chromosome pseudoautosomal regions (PAR) or the Y chromosome entirely depending on the sex chromosome complement of the samples for sequence realignment, rigorous variant calling and filtering strategies specific to the ploidy of each region of the X chromosome. We applied this workflow to 16,509 multi-ancestry samples from the Alzheimer's Disease Sequencing Project (ADSP). We performed an X-chromosome wide association study (XWAS) of common (minor allele frequency (MAF) >=0.01) single nucleotide polymorphism (SNPs) against four longitudinal cognitive and thirteen neuropathological traits harmonized by the ADSP Phenotype Harmonization Consortium (ADSP-PHC). Genetic associations were analyzed using GMMAT and GRAB controlling for sample relatedness and population stratification, followed by meta-analysis via GWAMA and metaUSAT. Different models were tested to account for X-inactivation states and identify sex-shared or sex-specific associations. We also performed genetic colocalization analyses to identify genes and tissues whose expression colocalized with the lead SNP using COLOC and HyPrColoc.

Results: After quality control, 15,237 unique individuals (6,089 males and 9,148 females) were included for XWAS. We analyzed 9,537 SNPs in the PAR and 193,464 in the non-PAR across 17 traits. We identified a novel genetic locus reaching genome-wide significance (P < 5.0E-8), with lead variant rs10521349 (chrX:71,132,567; AD risk AF = 0.27, omnibus P = 4.7E-9) located in the MED12 gene, showing effects shared by both sexes. Sex-stratified analyses further identified several sex-specific loci reaching X-wide significance (P < 1.0E-5). From genetic colocalization analysis, we identified several genes (MED12, FOXO4, and IL2RG) whose expression in whole blood and/or neutrophils colocalizes with the lead variant, rs12839587 (chrX:71,136,032).

Conclusions: This study demonstrates that SCC-informed alignment and variant calling combined with meta-analysis of harmonized quantitative traits significantly improves the power of genetic studies on sex chromosomes. Scaling this method to larger cohorts is warranted to further investigate the genetic drivers of sex-dimorphism in AD. The reported genetic loci and the associated genes also warrant in-depth study to elucidate their molecular mechanisms implicated in AD.

POSTER # 85

RETINAL VASCULAR COMPLEXITY ASYMMETRY AS A POTENTIAL BIOMARKER FOR PRECLINICAL ALZHEIMER'S GENETIC RISK. Zheng K, Dumkrieger G, Chen K, Woodruff B, Baxter L, Caselli RJ, Wang Y, Dumitrascu OM. Mayo Clinic Arizona; Arizona State University; Arizona Alzheimer's Consortium.

Background: The retina offers a non-invasive window for observing cerebral microcirculation and potentially neurodegeneration. Whereas retinal microvascular dysfunction in Alzheimer's disease (AD) has been previously reported the impact of APOE epsilon 4, the main AD genetic risk factor, on retinal neurovascular homeostasis is poorly understood. We investigate whether inter-eye asymmetry of retinal vascular fractal dimension (FD), can serve as a sensitive biomarker for preclinical AD risk.

Methods: We analyzed 294 cognitively normal participants stratified by APOE epsilon 4 status (154 non-carriers, 95 heterozygotes, 45 homozygotes). Retinal vascular FD was quantified from bilateral macula-centered fundus photographs across anatomical zones (B/C) and vessel types (artery/vein/combined) using the AutoMorph image-analysis pipeline. APOE genotype was classified as non-carrier, heterozygote, or homozygote based on epsilon 4 allele burden. Linear mixed-effects models adjusted for age and sex were used to evaluate APOE effects, eye effects, and APOE-by-eye interactions on retinal vascular FD metrics while accounting for within-subject correlations. Inter-ocular asymmetry (IoAs) was defined as the absolute difference in FD between left and right eyes (IoAs = |L - R|). Associations between APOE genotype and IoAs were evaluated using multivariable linear regression models with the non-carrier group as the reference category, adjusted for age and sex, from which regression coefficients (beta) and corresponding p values were estimated. Cohen's d effect-size were calculated. False discovery rate (FDR) correction was applied to control for multiple testing. Heterozygous and homozygous IoAs were compared via estimated marginal means.

Results: No significant APOE main effects on FD were observed after multiple-comparison correction for any anatomical zone or vessel type (p_FDR> 0.05). Although nominal APOE-by-eye interactions were detected within macular Zone C biomarkers, these associations did not survive multiple-comparison correction. The strongest interaction effect was observed for arterial FD in Zone C (interaction beta = 0.0332 for heterozygotes and beta = 0.0330 for homozygotes; p_FDR= 0.0702). In contrast, analysis of retinal interocular asymmetry identified significant APOE genotype-associated differences in macular Zone C arterial FD (p_FDR= 0.033). Compared with non-carriers, APOE epsilon 4 heterozygotes and homozygotes exhibited significantly greater asymmetry (beta_heterozygotes = 0.0284, p = 0.0022, p_FDR= 0.0402; beta_homozygotes = 0.0319, p = 0.0040, p_FDR= 0.0724, respectively). Effect sizes were moderate-to-large (Cohen's d = 0.75 for heterozygotes vs non-carriers and 0.84 for homozygotes vs non-carriers). No significant difference was detected between heterozygotes and homozygotes (p = 0.95).

Conclusions: APOE epsilon 4 carrier status is associated with increased retinal vascular interocular asymmetry (IoAs) despite minimal effects on retinal vascular complexity observable within a single eye. Increased asymmetry within macular Zone C arterial networks remained significant after multiple-comparison correction. Retinal asymmetry biomarkers may provide a scalable and noninvasive approach for identifying individuals at increased risk for preclinical AD-related neurodegenerative processes.

POSTER # 86

LIGHTING THE FUSE: ROSTRACE PET MAPS EARLY OXIDATIVE SPARKS THAT PRECEDE ALZHEIMER'S PATHOLOGY. Zhu Y, Hsieh CJ, Young A, Sheldon M, Kohli N, Gallagher E, Hou C, Li S, Lee H, Brinton R, Mach RH, McManus MJ. Children's Hospital of Philadelphia; University of Pennsylvania; University of Arizona; Arizona Alzheimer's Consortium.

Background: A global priority in neuroimaging is the noninvasive detection of early mitochondrial dysfunction and neuroinflammation, which drive the earliest stages of Alzheimer's disease (AD). Women experience a critical midlife bioenergetic transition during perimenopause that unmasks mitochondrial vulnerability linked to late-onset AD (LOAD). Noninvasive tools are urgently needed to identify at-risk individuals during this window and guide mitochondria-targeted interventions.

Methods: We evaluated [18F]ROStrace, a novel redox-sensitive PET probe, for in vivo detection of reactive oxygen species (ROS) and mitochondrial dysfunction across two complementary AD mouse models (APP/PS11 and hAPP-APOE3/4), with emphasis on sex, genotype, and midlife timing. We integrated metabolic phenotyping, dynamic PET/CT imaging, ex vivo validation, and spatially resolved transcriptomics (NanoString GeoMx) across preclinical to symptomatic ages.

Results: [18F]ROStrace retention distinguished AD model brains from controls by midlife, with significant increases preceding overt amyloid pathology and neuronal oxidative damage1. Retention was greater and emerged earlier in females in both APP/PS1 and hAPP-APOE4 models ($p < 0.001$), localizing to the hippocampus and cortex and correlating with amyloid burden. hAPP-APOE4 accelerated metabolic impairment (reduced mitochondrial content, O2 consumption, and activity) and increased vulnerability to immune challenge with LPS. Spatial transcriptomics in ROS-high regions revealed corresponding APOE4-dependent, cell-type specific signatures: microglial enrichment of neuroinflammatory and immune pathways; astrocytic signatures of mitochondrial dysfunction; and neuronal downregulation of synaptic transport.

Conclusions: Our data indicate that APOE4 and female sex lower the threshold for oxidative stress and glial reactivity during midlife. [18F]ROStrace PET noninvasively detects early mitochondrial inefficiency and associated neuroinflammation in female mice, highlighting the significance of perimenopause as a critical bioenergetic crisis for the at-risk AD brain.

By identifying this metabolic vulnerability before irreversible neurodegeneration occurs, ROStrace provides a powerful platform to stratify at-risk subjects and define therapeutic windows for mitochondria-directed interventions aimed at preventing progression to clinical AD.

POSTER # 87

[18F]SYNVEST-1 SV2A SYNAPTIC PET CLINICAL-BIOMARKER CHARACTERIZATION IN COGNITIVELY UNIMPAIRED AND EARLY AD/ADRD. Atri A, Serrano GE, Beach TG, Denkinger MN, Ashton NJ, Protas HD, Su Y, Sabandal M, Carson R, Spires-Jones T, Finnema S, FNIH SV2A PET Tracer Project Study Team. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Massachusetts General Brigham and Harvard Medical School; Biomarkers Consortium in Neuroscience, Foundation for the National Institutes of Health; Yale School of Medicine; University of Edinburgh; Abbvie R&D Discovery Research; Arizona Alzheimer's Consortium.

Background: Synaptic dysfunction, degeneration, and loss may represent a converging final common pathway through which Alzheimer's disease (AD) and related disorders (ADRD) produce cognitive and behavioral impairment. There is a critical need for robust biomarkers of synaptic density that, along with other biomarkers, inform prognosis and therapeutic responses in AD/ADRD. This synaptic vesicle glycoprotein-2A (SV2A) PET-autopsy validation study is part of a larger proof-of-concept study funded by the Foundation for the National Institutes of Health (FNIH) - that integrates plasma biomarkers, in vivo SV2A PET, ex vivo brain tissue measurements (e.g. radioligand binding and electron microscopy) and subsequent autopsy validation to assess the potential of SV2A-PET as a robust biomarker of synaptic density across the clinical spectrum of cognitively unimpaired (CU) MCI mild dementia with AD/ADRD.

Methods: Participants were recruited from the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND), a community-based longitudinal biomarker and brain donation program. The target sample size is N = 75 older adults spanning the clinical spectrum, including cognitively unimpaired (CU), mild cognitive impairment (MCI), and mild dementia due to Alzheimer's disease or related dementias (AD/ADRD). All participants undergo standardized clinical and neuropsychological assessments, along with multimodal biomarker collection, including SV2A PET imaging, structural MRI, and plasma-based AD-related biomarker profiling (including NULISA platforms). A subset (~50%) of the cohort additionally undergoes amyloid and tau PET imaging. All participants consent to brain donation. The program maintains a median postmortem interval of approximately 3 hours. Both frozen and fixed brain tissue samples are collected at autopsy. Postmortem synaptic density measures will be quantified and compared with in vivo SV2A PET imaging metrics.

Results: Sixty-six participants (CU, MCI, Dementia) underwent SV2A PET, MRI, and plasma biomarker assessment, with autopsy in six cases. Clinical severity increased across groups, with worsening cognition and function. SV2A PET showed a stepwise decline in tracer activity from CU to dementia, paralleled by higher pTau217/Aβ42 in dementia and variable GFAP. Autopsy confirmed high AD pathology in dementia, while some CU/MCI cases showed substantial pathology (≥Braak IV, intermediate ADNC). Histology demonstrated increased plaques and tangles with reduced MAP2, indicating neuronal loss in AD. Related work from the FNIH consortium further examines correlations between SV2A PET and synaptosome measures.

Conclusions: SV2A PET captures in vivo synaptic loss that tracks clinical severity and underlying AD pathology.

POSTER # 88

MULTISITE STUDY: PREDICTING LEWY BODY DISEASE USING SKIN BIOPSY ALPHA-SYNUCLEIN SEED AMPLIFICATION ASSAYS. Janarthanam C, Orrú CD, Hughson AG, Holzinger D,Taylor K, Kanthasamy AG, Caughey B, Heym RG, Adler CH, Shill HA, Mehta S, Driver-Dunckley E, Ho AH, Choudhury P, Shprecher DR, Belden CM, Atri A, Zhang N, Chen K, Serrano GE, Beach TG. University of Georgia; Laboratory of Neurological Infections and Immunity, Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases (NIAID); AbbVie Deutschland GmbH & Co.; AbbVie Bioresearch Center; Barrow Neurological Institute; Banner Sun Health Research Institute; Mayo Clinic Arizona; Arizona State University; Arizona Alzheimer's Consortium.

Background: Skin biopsies analyzed with α-synuclein seed amplification assays (SAA) might offer a simple way to determine the presence or absence of α-synuclein aggregates in patients with Lewy body disease (LBD). To date, though, the reported diagnostic accuracy of skin biopsies for PD, whether analyzed using immunohistochemistry (IHC) or SAA, has extensively varied between labs and methods, ranging from 24% to 98%.

Methods: We had blinded SAAs done in three independent laboratories to determine the accuracy of skin biopsy SAA in predicting the clinical diagnoses of Parkinson disease (PD; n = 23), PD with dementia (PDD; n =3) and dementia with Lewy bodies (DLB; n = 6). Subjects diagnosed with PD, PDD and DLB were analyzed together as Group 1, clinically unaffected subjects as Group 2 (n = 22) and those with risk factors for LBD as Group 3 (n = 51). Skin punch biopsies were taken from the posterior neck and four biopsies were analyzed in the 3 labs in 6 separate SAA's.

Results: Pairwise agreement between biopsies, labs and assays ranged from excellent (kappa 0.82) to moderate (kappa 0.40 - 0.68). Sensitivity across assays, labs and groups ranged between 50.0% and 65.6% while specificity ranged between 68.1% and 100%. Comparisons of Group 1 versus Group 2 produced the greatest specificities, between 77.3% and 100%, but with a maximum sensitivity of 61.3%. Exploratory analyses indicated that sensitivity for PDD and DLB was better (9/11 subjects positive in at least one assay; 81.8%), as was Group 3 sensitivity in subjects with both hyposmia and RBD (6/6). In 17 cases that subsequently came to autopsy, 93% of SAAs were positive in those at the neocortical LBD stage as compared to only 8% at any lower stage.

Conclusions: Skin biopsy α-synuclein SAA may be useful as a diagnostic and progression biomarker in Lewy body dementia clinical trials.

POSTER # 89

BRAIN-ONLY VERSUS GUT-ONLY A-SYNUCLEINOPATHY: A COMPREHENSIVE AUTOPSY SURVEY WITH BOTH IMMUNOHISTOCHEMISTRY AND SEEDING ASSAYS. Orru CD, Beach TG, Adler CH, Shilld HA, Driver-Dunckley E, Mehta SH, Atri A, Lorenzini I, Qiji SH, Intorcia AJ, Hughson AG, Groveman BR, King S, Alam P, Parveen S, Vascellari S, Caugheya B, Serrano GE. Laboratory Of Neurological Infections and Immunity, Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases (NIAID); Banner Sun Health Research Institute; Mayo Clinic Arizona; Barrow Neurological Institute; University of Cagliari; Arizona Alzheimer's Consortium.

Background: Braak and others have proposed that alpha-synuclein pathology (ASP) in Parkinson's disease (PD) may arise not only in the brain but alternatively from an initial site in the gastrointestinal (GI) tract, with subsequent passage to the central nervous system (CNS) through the vagus nerve or other routes.

Methods: We tested this hypothesis by using RT- QuIC, a form of alpha-synuclein seed amplification assay (SAA), to detect alpha-synuclein aggregates in 1,780 samples from 10 GI tract sites taken from autopsies of 50 PD subjects as well as 34 with CNS incidental Lewy body disease (ILBD) and 94 with no Lewy body (NLB) immunohistochemical (IHC) brain pathology.

Results: A positive SAA result was restricted to the GI tract in only 2 subjects, while SAA- or IHC-detected ASP was restricted to the brain in 11 subjects.

Conclusions: These results suggest that brain-only ASP is at least 5.5 times more common than GI-only ASP.

POSTER # 90

AUTOPSY VALIDATION OF CSF A-SYNUCLEIN SEED AMPLIFICATION DEMONSTRATES ROBUST DETECTION OF LEWY BODY PATHOLOGY AND TYPE 2 PROFILES ASSOCIATED WITH CSF COMPOSITION. Serrano GE, Zhang N, Walker J, Adler CH, Choudhury P, Shill HA, Mehta S, Driver-Dunckley E, Lorenzini I, Qiji SH, Campbell A, Aslam S, McHattie R, Krupp A, Intorcia AJ, Borja CI, Shull A, Wermager ZR, Mariner M, Belden CM, Atri A, Beach TG. Banner Sun Health Research Institute; Mayo Clinic Arizona; Barrow Neurological Institute; Brigham and Women's Hospital; Harvard Medical School; Arizona Alzheimer's Consortium.

Background: Parkinson disease (PD) and dementia with Lewy bodies (DLB), are characterized by misfolded α-synuclein accumulation, and because this pathology begins years before symptoms, biomarkers that detect it in life are increasingly critical for early diagnosis, biological classification, and clinical trial enrollment. This study aims to evaluate and validate the clinicopathological performance of postmortem cerebrospinal fluid (CSF) α-synuclein seed amplification assay (SAA) against autopsy-confirmed brain Lewy body pathology, determine the influence of coexistent Alzheimer disease (AD) pathology on assay performance, and investigate the neuropathological and biochemical correlations of distinct SAA seeding profiles.

Methods: We analyzed postmortem CSF SAA from 436 participants from the Arizona Study of Aging and Neurodegenerative Disorders with longitudinal clinical characterization, standardized neuropathological examination. Participants included those with PD, DLB, AD with Lewy bodies (ADLB), incidental Lewy body disease (ILBD), and cognitively normal controls. CSF was collected after calvarial removal, manual separation of the in-situ hemispheres and insertion of an 18-gauge needle with syringe into the lateral ventricles through the corpus callosum, taking care to avoid brain gray matter. CSF samples were centrifuged and were not subject to freeze-thaw cycles prior to SAA or biomarker analysis. CSF α-synuclein SAA results were compared with brain Lewy body burden and stage, AD neuropathology, and CSF biomarkers reflecting protein content and blood contamination. Positive α-synuclein SAA cases were further classified by Amprion as Type 1 or Type 2 based on seeding kinetics. Multivariable logistic regression models were then used to evaluate independent neuropathological predictors of SAA positivity.

Results: CSF α-synuclein SAA demonstrated excellent sensitivity for autopsy-confirmed Lewy body disease and closely tracked Lewy body burden and pathological stage but had limited specificity due to positive results in subjects without brain Lewy pathology. Weak negative associations were found with both amyloid plaque and neurofibrillary tangle burden. Among positive samples, Type 2 profiles were numerous despite the absence of autopsy-confirmed MSA microscopic changes and were associated with elevated hemoglobin, albumin, apolipoprotein A, total protein, and other indicators of altered CSF composition.

Conclusions: The Amprion CSF α-synuclein SAA, as administered in this study, has apparently high sensitivity and a strong correlation with all brain stages and load of autopsy-confirmed Lewy body pathology but this is marred by only moderate specificity. Comorbid AD pathology is not a significant predictor of a positive SAA test. Type 2 profiles were relatively numerous despite the absence of subjects with autopsy evidence of MSA, but were associated with altered CSF composition, suggesting that pre-analytical sample characteristics may influence the differing assay kinetics used to define the two result types. Study limitations include that approximately one-third of control individuals without Lewy body pathology tested SAA-positive, suggesting that at least some of these results may reflect technical false positives rather than a true biological signal. In addition, SAA provides a binary classification and does not quantify the burden of α-synuclein pathology. Further longitudinal, inter-laboratory, and autopsy-confirmed studies are needed to establish the reproducibility, specificity, and biological significance of these findings.

POSTER # 91

OLFACTORY DECLINE IN AGING: LONGITUDINAL TRAJECTORIES AND ASSOCIATIONS WITH COGNITIVE DECLINE AND POSTMORTEM NEUROPATHOLOGY. Tremblay C, Choudhury P, Driver-Dunckley E, Alasmar Z, Serrano GE, Shill HA, Mehta S, Ho A, Fereshtehnejad SM, Shprecher D, Lorenzini I, Belden CM, Atri A, Adler CH, Beach TG, Dadar M, Zeighami Y. Douglas Mental Health University Institute; McGill University; Banner Sun Health Research Institute; Mayo Clinic Arizona; Barrow Neurological Institute; University of British Columbia; Karolinska Institutet; Arizona Alzheimer's Consortium.

Background: Decline in olfactory function may be used as a predictor of cognitive decline, to enhance early detection models, improve risk stratification, and enable early intervention.

Methods: Design, setting and participants: Retrospective longitudinal analysis with clinicopathological correlations of a prospective population-based cohort study using data from the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) and its Brain and Body Donation Program.
Participants included cognitively unimpaired individuals without parkinsonism that converted to mild cognitive impairment (MCI) and/or dementia or remained cognitively stable. Main Outcomes and Measures: longitudinal change in olfaction, neuropsychiatric symptoms, motor function and memory, conversion to MCI/dementia, postmortem neuropathology.

Results: Over a mean follow-up period of 7.7 ± 5.4 years, out of 922 participants who were cognitively unimpaired at the first cognitive conference, 643 remained cognitively unimpaired, 279 converted to MCI, and 82 developed dementia. Of these, 633 individuals had at least 2 olfactory tests. Converters showed reduced olfactory function ($t=-12.6$, $p < 0.001$), and faster decline in memory ($t= -7.33$, $p < 0.01$) and amyloid plaque burden ($t= -2.85$, $p < 0.005$) and a faster decline over time was associated with a higher burden of tau ($t=5.66$, $p<0.0001$).

Conclusions: A reduction in olfactory identification ability is observed up to a decade prior to conversion to MCI and is associated with underlying burden of neuropathology markers, underscoring the value of incorporating olfactory testing in cognitively unimpaired individuals to identify those at-risk of future cognitive decline.

POSTER # 92

QUANTITATIVE DIGITAL VERSUS SEMI-QUANTITATIVE ASSESSMENTS OF TAU PATHOLOGY IN CORRELATION WITH IN VIVO TAU PET REGIONAL SUVR. Tremblay C, Freiburghaus T, Pawlik D, Hauer KO, Serrano GE, Zeighami Y, Dadar M, Intorcia AJ, Ossenkoppele R, Pontecorvo MJ, Hansson O, Smith R, Beach TG. Douglas Mental Health University Institute; McGill University; Banner Sun Health Research Institute; Lund University; Office for Psychiatry and Habilitation, Psychiatric Clinic Lund; Memory Clinic, Skåne University Hospital; Eli Lilly and Company; Vrije Universiteit Amsterdam; Amsterdam Neuroscience, Neurodegeneration; Arizona Alzheimer's Consortium.

Background: Quantitative digital image analysis has emerged as a powerful tool for assessing neuropathological burden. However, relatively few studies have directly compared digital pathology quantification with conventional semi-quantitative gradings or evaluated their respective relationships with in vivo biomarkers.

Methods: We compared quantitative digital pathology quantification and semi-quantitative regional gradings of phosphorylated tau (ptau) immunohistochemical staining and assessed their correlations with regional in vivo [18F]flortaucipir standardized uptake value ratios (SUVRs) in 52 cases from the AVID A16 end-of-life study.

Results: Digital pathology quantification and semi-quantitative gradings of ptau were strongly correlated across all 19 cortical and mesial temporal regions examined (Spearman’s rho range: 0.6-0.9; all $P < 0.0001$). Both approaches showed similarly robust associations with regionally corresponding tau PET SUVRs. Direct comparison of matched correlation coefficients revealed stronger PET-pathology associations for the digital quantification in the left amygdala and the inferior parietal lobule. Overall, digital pathology quantification and semi-quantitative assessments of ptau pathology yielded highly comparable results, both in the quantification of regional pathology burden and in their relationships with tau PET measures.

Conclusions: These findings suggest that semi-quantitative pathology gradings remain a valid and informative approach for clinicopathological correlation studies, while supporting the use of digital pathology quantification methods.

Arizona Alzheimer's Consortium
27th Annual Scientific Conference

Student Poster Presentation

Abstracts

STUDENT POSTER # 93

INTERACTION OF VEGF GENETIC VARIANTS AND APOE EPSILON 4 ON PLASMA TAU BIOMARKERS IN COGNITIVELY UNIMPAIRED OLDER ADULTS. Abow Alkhier A, Malek-Ahmadi M, Piras I, Wang Q, Chen K, Devadas V, Luo J, Su Y, Marques T, Denkinger MN, Singh A, Ashton NJ. Arizona State University; Banner Alzheimer's Institute; Translational Genomics Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: The Apolipoprotein E epsilon 4 allele is the primary genetic risk factor for late-onset Alzheimer's disease, yet its phenotypic expression is highly variable. Vascular endothelial growth factor (VEGF) regulates angiogenesis and blood-brain barrier integrity, processes relevant to the clearance of toxic proteins from the brain. Whether specific VEGF genetic variants modify the relationship between APOE epsilon 4 and tau biomarkers in the preclinical stage of neurodegeneration remains poorly characterized. This study examined the interactive effects of vascular genetic variants and APOE epsilon 4 status on plasma-based tau biomarkers in cognitively unimpaired older adults.

Methods: Cross-sectional data from cognitively unimpaired older adults enrolled in the Alzheimer's Disease Neuroimaging Initiative cohort were evaluated (N of 245 for VEGF models; N of 229 for MTHFR models). To account for the right-skewed distribution of blood-derived biomarkers, generalized linear models with a Gamma distribution and a log link were used. Interaction terms were constructed between APOE epsilon 4 carrier status and four vascular variants (VEGF 1154A, VEGF 2578C, MTHFR 677T, and MTHFR 1298C) across brain-derived and standard plasma tau outcomes. All models adjusted for age, sex, and education. Benjamini-Hochberg false discovery rate correction was applied across the brain-derived tau interaction tests. Subgroup effect sizes were estimated with Cohen's d using the within-group standard deviation of the observed biomarker values.

Results: A nominal interaction was observed between APOE epsilon 4 and VEGF 1154A on adjusted brain-derived p-tau-181 (Gamma p of 0.022). Among VEGF 1154A carriers, APOE epsilon 4 carriers showed higher brain-derived p-tau-181 than non-carriers (Cohen's d of 0.70), whereas among 1154A non-carriers the APOE epsilon 4-related difference was small (Cohen's d of 0.14). A consistent direction of effect was seen for the standard plasma p-tau-181 and p-tau-231 measures. A separate nominal interaction was observed between APOE epsilon 4 and VEGF 2578C on adjusted brain-derived MAPT (Gamma p of 0.029), in which the direction of the APOE epsilon 4 association differed by 2578C status (Cohen's d of 0.37 among 2578C non-carriers versus negative 0.20 among carriers). After Benjamini-Hochberg correction within the brain-derived assays, no interaction remained significant (smallest adjusted p of 0.19); results are therefore reported as exploratory. MTHFR variants showed no significant interactions.

Conclusions: In this exploratory analysis, VEGF genotype was associated with differing relationships between APOE epsilon 4 and brain-derived tau biomarkers in cognitively unimpaired older adults, with VEGF 1154A and VEGF 2578C showing distinct patterns of association. Because these interactions did not survive correction for multiple comparisons, they should be interpreted as hypothesis-generating and require replication in an independent cohort. If confirmed, variant-specific vascular profiles may inform multi-omic risk stratification for early intervention.

STUDENT POSTER # 94

DISCOVERY OF A "CORRECTOR" VIA HIGH-THROUGHPUT SCREENING TO NEGATE UNWANTED LXR-DRIVEN LIPOGENESIS IN LIVER. Alamb F, Outtena C, Ackerman-Berriera M, Reddy Velmaa G, Pentona C, Reddy Muskua S, Lahamb MS, Ranaa M, Maa N, Thulasingama S, Annaduraia A, Thatchera GRJ. University of Arizona; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is characterized by amyloid-β (Aβ) aggregation and tau pathology, with increasing evidence linking disrupted lipid metabolism to disease progression. Apolipoprotein E (ApoE), the primary apolipoprotein in the brain, must be properly lipidated to form HDL-like particles, a process mediated by the cholesterol transporter ABCA1. The APOE4 allele, the strongest genetic risk factor for AD, is associated with impaired lipid transport. ABCA1 expression is regulated by nuclear hormone receptors, particularly liver X receptor (LXR). Although LXR activation enhances ABCA1 expression and promotes reverse cholesterol transport, it also induces hepatic lipogenic genes via SREBP1c, leading to elevated triglycerides and LDL levels—posing a major therapeutic limitation.

Methods: To address this challenge, we developed a high-throughput screening (HTS) assay using a HepG2 cell line stably expressing an SRE-driven luciferase reporter to quantify SREBP1c-mediated transcription downstream of LXR activation. An FDA-approved small-molecule library was screened to identify "correctors" that suppress LXR-induced lipogenesis without compromising ABCA1 expression. Hits were counterscreened using a CCF ABCA1-luciferase assay to exclude compounds that inhibit the beneficial cholesterol efflux pathway. Lead candidates were validated in HepG2 and AML12 hepatocyte-derived cells via qPCR and western blotting to assess lipogenic markers (SREBP1c, FASN, ACC) and ABCA1 expression.

Results: We identified Avacopan, an FDA-approved C5a receptor antagonist, as a compound that selectively reduces LXR-induced lipogenic gene expression while preserving ABCA1 mRNA and protein levels. These findings were consistent across both cell lines.

Conclusions: Together, these studies provide proof-of-concept for a "corrector" strategy that uncouples adverse lipogenesis from beneficial ABCA1-mediated cholesterol efflux, offering a promising therapeutic approach for lipid-associated neurodegenerative diseases such as AD.

STUDENT POSTER # 95

PLASMA P-TAU217 AND WHITE MATTER HYPERINTENSITY NETWORK PATTERN PREDICTS MEMORY RETENTION IN OLDER ADULTS AT RISK FOR ALZHEIMER'S DISEASE. Ally M, Bharadwaj PK, Schade RN, O'Shea A, Rayaprolu S, Rodriguez K, Gertler J, Nelson I, Katta S, Huo Z, Habeck CG, DeKosky ST, Woods AJ, Bowers D, Alexander GE. University of Arizona; University of Florida; Columbia University; University of Texas at Dallas; Arizona Alzheimer's Consortium.

Background: Plasma phosphorylated tau 217 (p-tau217) is a sensitive biomarker of early Alzheimer's disease (AD) pathology, but its relationship with brain and cognitive aging has yet to be fully investigated. White matter hyperintensities (WMHs) on magnetic resonance imaging (MRI) reflect small vessel cerebrovascular disease (svCVD) and are prevalent in aging. Greater WMH burden has been associated with cognitive decline, increased dementia risk, and, more recently, elevated plasma p-tau217. As WMHs are not uniformly distributed, we sought to identify a regional WMH volume (rWMHV) network pattern related to plasma p-tau217 and to examine its relationship with demographic, clinical, and cognitive variables in healthy older adults with elevated AD dementia risk.

Methods: Participants were 154 community-dwelling older adults (age=70.9±4.8 years; M/F=59/95; apolipoprotein E [APOE] e4 carrier y/n=58/96; site UA/UF=76/78) with subjective cognitive complaints and family history of dementia, screened to exclude cognitive impairment and major comorbidities, including kidney disease. Plasma p-tau217 was measured using Quanterix Simoa. rWMHV was quantified from T1 and FLAIR MRI using the Lesion Segmentation Toolbox with SPM12 and FreeSurfer. Measures of memory, executive function, and processing speed were included. Multivariate network covariance analysis, using the Scaled Subprofile Model (SSM) with 10,000 bootstrap iterations, identified a p-tau217-related rWMHV network pattern. Multiple regression examined associations of imaging (total intracranial volume, site), demographic (age, sex, race/ethnicity, education), and clinical (APOE e4, hypertension) covariates with SSM pattern scores. Linear regression tested associations between pattern scores and cognition, with covariate adjustment and false discovery rate (FDR) correction ($p<.05$).

Results: The SSM identified a p-tau217-rWMHV network pattern characterized by greater WMH volume in bilateral temporal and left parietal regions with relative reductions in bilateral frontal, cerebellar, and brainstem areas ($R2=0.073$, $p=7.234E-4$). Among covariates, only older age predicted greater pattern expression (beta=0.359, FDRp=5.501E-5). After adjustment for demographic and clinical covariates, increased pattern expression was related to worse Logical Memory retention (beta=-0.245, FDRp=.015), but not with other cognitive measures.

Conclusions: In healthy older adults with elevated AD dementia risk, plasma p-tau217 was related to a rWMHV network pattern, preferentially involving temporoparietal brain regions, whose expression was associated with older age and distinctly predicted worse memory retention. These findings further support a link between cerebrovascular brain health and the development of early AD pathology in the context of cognitive aging.

STUDENT POSTER # 96

IMPACT OF ASYMPTOMATIC EXTRACRANIAL CAROTID ARTERY DISEASE ON STRUCTURAL BRAIN CONNECTOME INTEGRITY. Altekreeti M, Wiskoski H, Ugonna C, Arias J, Trouard T, Weinkauf C. University of Arizona; Arizona Alzheimer's Consortium.

Background: Extracranial carotid artery disease (ECAD) affects approximately 15 percent of adults over 60 years of age and is a major risk factor for ischemic stroke. More than 45 billion dollars are spent annually in the United States on the diagnosis and treatment of stroke and transient ischemic attacks. While carotid artery disease ECAD is associated with cerebrovascular events, it has also been linked to increased Alzheimer's disease risk and poorer cognitive outcomes. The impact of ECAD on structural brain connectivity prior to symptomatic stroke remains incompletely understood. This study investigated whether asymptomatic extracranial carotid artery disease ECAD (aECAD), which is, ECAD in the absence of stroke or TIA, is associated with alterations in structural brain connectome integrity

Methods: A total of 116 participants from the Carotids and Minds Magnetic Resonance Imaging and Cognitive Assessment Study (NIH R01 AG070987) were included following quality assessment of multi-shell diffusion magnetic resonance imaging (dMRI) data (62 aECAD, 54 controls). Diffusion MRI data were preprocessed using QSIPrep and postprocessed using the MRtrix structural connectome pipeline, including fiber orientation distribution (FOD) generation, anatomically constrained tractography, and SIFT2 filtering. Structural connectomes were generated using FreeSurfer-based brain parcellations, and connectivity strength was quantified using logarithmically transformed fiber bundle capacity (FBC). Global, intrahemispheric, and interhemispheric connectivity metrics were compared between groups. Associations among age, stenosis severity, connectivity measures, and cognitive performance were also evaluated.

Results: Increasing age was associated with greater stenosis burden ($r = 0.18$, $p = 0.029$), lower structural connectivity ($r = -0.46$, $p = 2.05e-7$), and reduced cognitive performance ($r = -0.27$, $p = 0.0016$), with structural connectivity demonstrating the strongest age-related effect. Participants with aECAD demonstrated significantly lower global structural connectivity strength compared with controls ($p = 0.023$). Significant reductions were also observed in interhemispheric connectivity ($p = 0.037$) and intrahemispheric connectivity ($p = 0.039$), indicating widespread network disruption. No significant differences were observed between ipsilateral and contralateral hemispheres, suggesting that connectivity alterations were not confined to the side of greatest stenosis. Maximum percent carotid stenosis was not significantly associated with connectivity measures.

Conclusions: aECAD is associated with reduced structural brain connectivity and evidence of widespread network disruption as assessed. Significant reductions in global, intrahemispheric, and interhemispheric connectivity were observed. These findings provide insight into potential mechanisms linking vascular disease and cognitive decline. Future work will investigate the relationship between structural and functional connectivity using resting-state functional MRI and will include younger healthy control cohorts to better distinguish disease-related effects from normal aging.

STUDENT POSTER # 97

DIGITAL STORYTELLING FOR CAREGIVER ADAPTATION VIA MEANING-MAKING (DST-CAMM): A THEORY-DRIVEN FRAMEWORK TO SUPPORT DEMENTIA CAREGIVERS' WELL-BEING. Bahrami R, Fleury J, Kim SW. Arizona State University; Arizona Alzheimer's Consortium.

Background: With the U.S. population aging rapidly, dementia has become a significant public health issue that requires continuous care and supervision. As of 2026, more than seven million Americans aged 65 and older are living with dementia. Almost 13 million unpaid caregivers, primarily family members, are providing ongoing care for them, who are at risk for diminished well-being driven by disruption in coherence, purpose, and mattering, the three core dimensions of meaning in life. Evidence shows that caregivers' ability to reconstruct meaning in their caregiving role has a significant impact on well-being. Digital storytelling (DST) through which emotionally significant experiences may be explored and expressed as coherent, meaningful stories. However, the theoretical foundations of DST interventions are insufficiently specified. Guided by Sidani's (2020) recommendations for reporting intervention's theory, this study introduced the Digital Storytelling for Caregiver Adaptation via Meaning-Making (DST-CAMM) model, a theory-driven framework designed to operationalize meaning-making processes and specify pathways through which DST may support caregiver well-being.

Methods: Model Logic: DST-CAMM integrates the meaning-making model and narrative theory to establish a comprehensive foundation for intervention theory. Based on the meaning-making model, caregiving challenges can create discrepancies between global and situational meaning, which may prompt efforts to restore meaning through reappraisal. Narrative theory extends this process by positioning storytelling as a mechanism through which individuals may reorganize experiences and reconstruct meaning. DST-CAMM has three core components: (1) story circles and narrative development, which are intended to support coherence, (2) digital story production, which may support a sense of purpose, and (3) group sharing and reflection that may promote experiences of mattering through validation and connection. Reappraisal is proposed as the central mechanism of action and operates through cognitive (redefining caregiving experiences), affective (supports emotional processing), and social (peer validation) pathways. Additionally, contextual factors such as cultural values, caregiving norms, facilitator competence, and group safety are essential considerations for engagement and outcomes.

Results: The proposed meaning-making process in the DST-CAMM model involves alignment between intervention components, hypothesized mechanisms of action, and expected outcomes. Therefore, the DST-CAMM model provides a framework for operationalizing abstract constructs of meaning into observable and potentially replicable practices that may support caregiver well-being.

Conclusions: DST-CAMM provides a theoretically grounded framework for understanding how digital storytelling may promote meaning-making and well-being among dementia family caregivers. By identifying reappraisal as a hypothesized mechanism of action and linking specific intervention components to coherence, purpose, and mattering, DST-CAMM may offer practical implications for intervention development and future empirical testing.

STUDENT POSTER # 98

DIGITAL STORYTELLING IN DEMENTIA CARE: A SCOPING REVIEW. Bahrami R, Gómez-Morales A, Kim SW. Arizona State University; Arizona Alzheimer's Consortium.

Background: Digital storytelling has emerged as an increasingly recognized narrative-based approach in dementia care. Despite growing interest, research remains conceptually and methodologically fragmented, with considerable variation in storytelling approaches. This scoping review aimed to map the existing literature by synthesizing digital storytelling approaches, implementation characteristics, reported contributions, and evidence gaps.

Methods: This scoping review followed the Joanna Briggs Institute methodology and was reported in accordance with the PRISMA-ScR. Electronic databases, including PubMed, CINAHL, and PsycINFO, were searched and supplemented by backward citation searching. English-language literature evaluating digital storytelling or related multimedia narrative approaches was searched without time restriction and screened for eligibility. Data were charted using a standardized extraction form and synthesized descriptively using narrative and thematic approaches.

Results: Thirteen studies published between 2012 and 2025 met the inclusion criteria. Based on findings, digital storytelling approaches varied substantially in technologies used, implementation procedures, participant involvement, and care settings, highlighting the absence of a standardized intervention model. Five recurring applications were identified: (1) preserving identity and personhood, (2) enhancing communication, (3) strengthening relationships through shared storytelling, (4) supporting person-centered dementia care, and (5) promoting social participation and engagement. The review revealed an evolution of digital storytelling from individualized story creation toward broader applications supporting implementation and routine dementia care. Major evidence gaps included limited theoretical foundations, methodological heterogeneity, underrepresentation of family caregivers, and insufficient attention to equity, accessibility, and implementation.

Conclusions: Digital storytelling represents a flexible, narrative-based approach that has the potential to enhance dementia care, such as person-centered care. Future research should focus on strengthening the theoretical foundations of digital storytelling, examining the mechanisms by which digital storytelling achieves its effects, improving consistency in research methodologies, evaluating its implementation in routine practice, and developing more equitable strategies for both individuals with dementia and their caregivers. This will help establish digital storytelling as an evidence-based and theory-informed component of dementia care.

STUDENT POSTER # 99

MEANING-MAKING THROUGH DIGITAL STORYTELLING FOR FAMILY CAREGIVERS OF INDIVIDUALS WITH DEMENTIA. Bahrami R, Gómez-Morales A, Kim SW. Arizona State University; Arizona Alzheimer's Consortium.

Background: Family caregivers of individuals living with dementia frequently experience challenges that disrupt their sense of coherence, purpose, and mattering, contributing to an increased risk of diminished psychological well-being. Meaning-making has been identified as an important adaptive process that helps individuals interpret and integrate difficult life experiences and improve psychological well-being. However, little is known about how meaning-making occurs within caregiving interventions. To address this gap, we developed a theory-driven conceptual framework, Digital Storytelling for Caregiver Adaptation via Meaning-Making (DST-CAMM), which integrates meaning-making and narrative theories to support caregiver adaptation and meaning-making through digital storytelling (DST). Guided by the DST-CAMM model, this study aims to (1) explore how dementia family caregivers describe experiences of caregiving distress, adaptation, and meaning reconstruction through the process of digital story creation and (2) develop caregiver-generated digital stories that can serve as intervention materials for future implementations of the DST intervention.

Methods: A mixed-methods formative study using a single-group pre-post design will be conducted with adult family caregivers of individuals with dementia (N = 6) residing in the Phoenix metropolitan area. Eligible participants will be English-speaking caregivers with substantial caregiving experience and caregiving-related experiences relevant to meaning-making. Participants will attend a two-day, in-person DST workshop led by a DST-certified facilitator. The first day will focus on story circle and narrative development, during which caregivers will be asked to share their caregiving experiences using specific prompts. The second day will involve digital story production, story sharing, and guided reflection. Survey data will be collected before and immediately after the workshop. Quantitative measures will assess meaning in life using the Multidimensional Existential Meaning Scale. The meaning-making process, with reappraisal as the core mechanism of change, will be measured using the Emotion Regulation Questionnaire, the State Reappraisal Inventory, and the Interpersonal Emotion Regulation Questionnaire Scales, representing cognitive, affective, and social dimensions of reappraisal. Intervention acceptability will be assessed using the Acceptability of Intervention Measure. A post-workshop focus group will be conducted to further explore participants' experiences of meaning-making and their perceptions of the intervention process.

Results: Participants are expected to report improvements in their sense of coherence, purpose, and mattering following the two-day DST workshop. Reappraisal is anticipated to emerge as an important process through which DST facilitates meaning-making. Findings will provide preliminary evidence supporting the DST-CAMM framework and will guide the development of the theory-based DST intervention for future pilot randomized studies.

Conclusions: Findings will provide preliminary evidence supporting the DST-CAMM framework and will guide the development of the theory-based DST intervention for future pilot randomized studies.

STUDENT POSTER # 100

PRESERVED METAPHOR COMPREHENSION DESPITE SEVERE LITERAL LANGUAGE IMPAIRMENT IN SEMANTIC VARIANT PPA: EVIDENCE FOR GRADED DEGRADATION OF SEMANTIC KNOWLEDGE. Baiocco L, Nickels K, Lai VT, Kielar A. University of Arizona; Arizona Alzheimer's Consortium.

Background: The semantic variant of Primary Progressive Aphasia (svPPA) is a neurodegenerative language disorder characterized by the gradual loss of word meaning and degradation of conceptual and object knowledge (Mesulam et al., 2009). Although the core symptoms of svPPA are well-characterized in the literature, to date, little is known about how such linguistic deficits impact metaphorical language processing. Metaphors (e.g., "lawyers are sharks") involve two different concepts that need to be accessed: the source ("sharks") and the target meaning ("aggressive"). Due to this complex conceptual nature, we hypothesized that metaphorical comprehension would be impaired in a participant diagnosed with svPPA relative to healthy older adults.

Methods: A 58-year-old woman diagnosed with svPPA and 12 healthy controls (Mage = 68, SD = 7.7) completed cognitive-linguistic assessments and a computerized metaphor comprehension task (Klooster et al., 2020) consisting of 16 multiple-choice questions. Each question had a target sentence, either metaphoric or literal (e.g., "The summer romance/construction was a merry-go-round."), with possible 4 answers (for metaphoric: dizzying delight/amusement ride/serious punishment/brick fireplace; for literal: colorful carousel/real estate/moldy dungeon/grocery cart). Participants were asked to select the answer that most appropriately matched the meaning of the target sentence. The metaphoric and literal pairs were matched for familiarity, naturalness, frequency, and valence (Cardillo et al., 2017). For the 4 answer choices, we collected ratings of familiarity, imageability, valence, and arousal for analyses.

Results: Contrary to our hypothesis, metaphoric sentence comprehension (90% accuracy) was spared in our participant with svPPA, falling just below the control mean (95.8%, SD = 6.1%). In contrast, svPPA scored extremely poorly on literal sentence comprehension (55.5% accuracy), more than 6 standard deviations below the control mean (94.8%, SD = 6.4%), indicating severe impairment. A Revised Standardized Difference Test (Crawford & Garthwaite, 2005; Crawford et al., 2010), revealed that the clinical dissociation between the metaphoric and literal scores in svPPA was statistically significant ($t(11) = 3.010$, $p = .012$). Additionally, a linear mixed model revealed answer option familiarity as a significant predictor of accuracy for the control group ($\beta = 1.32$, $SE = .43$, $p = .002$), but only marginally so for svPPA ($\beta = 1.89$, $SE = 1.06$, $p = .076$).

Conclusions: In this svPPA patient, despite impaired precise and fine-grained lexical-semantic representations tied to anterior temporal lobe dysfunction, metaphoric ability was preserved, suggesting that figurative language processing may be supported by coarser, more holistic semantic representations and/or engagement of associative contextual or pragmatic processes. Item analyses also indicated that the patient relied less on item familiarity than controls in selecting the correct answer. Our results suggest that meaning representations are not uniformly impaired in svPPA, motivating the probing of metaphor-based interventions to slow loss of semantic knowledge in svPPA.

STUDENT POSTER # 101

REVERSE-TRANSLATION OF REAL-WORLD MENOPAUSAL HORMONE THERAPY DATA WITH A HUMANIZED APP/APOE ALZHEIMER'S DISEASE RISK MOUSE MODEL. Bantugan MA, Ragsdale S, Kalina A, Vitali F, Wang T, Brinton R. University of Arizona; Arizona Alzheimer's Consortium

Background: Alzheimer's disease (AD) is a major public health challenge that disproportionately affects women, who account for nearly two-thirds of diagnosed cases. Despite this disparity, sex-specific risk factors and therapeutic strategies remain underexplored. The menopausal transition, characterized by a decline in ovarian estrogen production, has been implicated as a critical window of vulnerability for AD risk. Menopausal hormone therapies (MHTs) have therefore emerged as promising candidates for mitigating AD development. However, the translatability of the most commonly prescribed MHT to mechanistic outcomes in a preclinical genetic risk model of AD remains poorly defined.

Methods: We employed a reverse-translational framework integrating real-world health insurance data with experimental studies in a genetic mouse model of AD-risk. The US-based Mariner claim database was utilized to identify women prescribed MHTs and characterized therapy formulation and age at initiation. Sensitivity analyses evaluated associations between MHT class, initiation timing, and AD incidence. Guided by population-level findings indicating estrogen-based therapies as the predominant MHT class, we conducted preclinical studies in 14-month-old female humanized APP/APOE mice. Animals received subcutaneous 60-day slow-release 17β-estradiol (0.09 mg/pellet) for 30 days or sham treatment. To model clinically relevant initiation windows, both regular and irregular cyclers were randomized to treatment or sham. Metabolic and physiological outcomes commonly disrupted in both AD and menopause, including fasting blood glucose and ketones, body composition (assessed by EchoMRI), and cycling status, were assessed before tissue collection.

Results: Medical informatics analyses of insurance claims data revealed distinct AD risk profiles across MHT classes, with earlier initiation of therapy (before age 60) associated with lower AD odds compared to later initiation. Estrogen-based therapies represented the predominant class of prescribed MHTs with estrogen-progestogen combined representing 12% of MHT users. In parallel, preclinical studies suggested that estrogenic interventions modulate biological pathways implicated in AD and menopause, including reduced body weight by 34% ($p<0.05$). Other assessed outcomes reflective of menopausal pathway changes did not differ by treatment.

Conclusions: By correlating population-level patterns of MHT use with targeted interventions in a genetic AD risk model, this work informs ongoing studies aimed at elucidating the biological pathways implicated in the most translationally relevant window of elevated AD risk in women.

STUDENT POSTER # 102

PS19 MICE TREATED WITH THE NOVEL INHIBITOR, DYR533, SHOW ATTENUATED TAU PATHOLOGY, NEUROINFLAMMATION, RNA PROCESSING AND SYNAPTIC FUNCTION.

Bartholomew S, Winslow W, Hansen N, Martinez M, Watkins K, Sharma R, Mackler N, Hulme C, Dunckley T, Pirotte P, Velazquez R. Arizona State University; Integrated Mass Spectrometry Shared Resources, City of Hope Comprehensive Cancer Center; Translational Genomics Research Institute; University of Arizona; Arizona Alzheimer's Consortium.

Background: The prevalence of Alzheimer's Disease (AD) and Related Dementias (ADRD) are increasing, emphasizing a need for effective therapeutic interventions. Inhibiting kinases that promote tau pathology and neuroinflammation, such as Dual-specificity tyrosine-phosphorylation related kinase 1a (Dyrk1a), are promising. We found elevated Dyrk1a expression in primary tauopathy post-mortem brain compared to healthy controls.

Methods: We developed a novel, highly selective Dyrk1a inhibitor (DYR533) which significantly reduced tau hyperphosphorylation at multiple pathological epitopes and attenuated neuroinflammation in the PSS19 tauopathy mouse model (Tg). We performed comparative hippocampal (Hp) tissue proteomics of Tg mice treated with increasing dose of DYR533 (1.0 and 5.0 mg/kg) against untreated vehicle controls (Tg and NonTg mice).

Results: Overall, we identified 6,513 proteins with Washc2—an endosomal sorting and transport protein— being significantly (adj. p-value <0.05) upregulated in the 5.0 mg/kg Hp group versus Tg vehicle. Gene set enrichment analysis revealed DYR533 treatment enriched processes involved in RNA processing and pre- and post-synaptic function in Tg mice. Consistent with these findings, Dyrk1a is known to be involved in mRNA splicing which contributes to the 3R/4R ratio disruption often seen in ADRD. Additionally, Dyrk1a overexpression has been shown to impair NMDA receptor–dependent long-term potentiation, suggesting that DYR533 treatment may influence proteins driving synaptic deficits. Conversely, immune system activation and regulation, apoptosis and stress response gene sets were depleted.

Conclusions: Together, our data identify DYR533 as a modulator of tau pathology that alters proteins related to key ADRD-relevant processes, including RNA processing and synaptic function. Our ongoing studies are aimed at defining the underlying cellular mechanisms and cell specific functions of Dyrk1a within the brain.

STUDENT POSTER # 103

MEDICATION NON-ADHERENCE IN COMORBID HYPERTENSION AND DIABETES SELECTIVELY PREDICTS VASCULAR DEMENTIA WITH DISTINCT PERIPHERAL BIOMARKER SIGNATURES. Belnavis A, Stecher C, Chen K, Chiu S, Ofori E. Arizona State University; Banner Alzheimer's Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Hypertension (HTN) and type 2 diabetes mellitus (T2DM) are the two most prevalent modifiable risk factors for dementia, yet 27 to 50% of patients fail to adhere to prescribed medications. Whether dual non-adherence selectively increases vascular dementia (VD) risk over Alzheimer's disease (AD), mild cognitive impairment (MCI), and other Alzheimer's disease-related dementias (ADRDs), and whether non-adherent individuals exhibit distinct peripheral biomarker profiles, remain uncharacterized. We hypothesized that dual non-adherence would increase vascular dementia risk without affecting AD, MCI, or other ADRD risk, producing a pro-inflammatory, pro-atherogenic biomarker signature.

Methods: Retrospective longitudinal analysis using the NIH All of Us Research Program (Controlled Tier v8). Adults 50 and older with comorbid HTN and T2DM, at least 2 prescription fills each of antihypertensive and antidiabetic medications within a 12-month baseline, at least 3 years follow-up, and no prior dementia were included (N=9,130; mean age 71.1 +/- 9.5; 52.9% female; mean follow-up 5.9 years). Adherence was assessed via proportion of days covered (PDC at least 0.80 = adherent): dual adherent (n=3,412; 37.4%), HTN-adherent/DM-non-adherent (n=1,518; 16.6%), HTN-non-adherent/DM-adherent (n=1,205; 13.2%), or dual non-adherent (n=2,995; 32.8%). Primary outcomes were incident VD and AD; secondary outcomes included MCI and other ADRDs. Modified Poisson regression with robust standard errors estimated prevalence ratios (PR) adjusting for age and sex. Twelve peripheral clinical protein biomarkers were extracted from EHR records within 1 year prior to baseline through end of follow-up and compared across adherence categories using Kruskal-Wallis tests.

Results: Among 504 dementia diagnoses, dual non-adherence was significantly associated with increased VD risk (PR=3.72, 95% CI: 1.89 –7.29, p<0.001), but not AD (PR=0.67, p=0.50) or MCI (PR=0.81, p=0.16). Unadjusted VD prevalence rates increased with the number of non-adherent medication classes (chi-square =19.53, p<0.001): dual adherent 0.32%, HTN-adherent/DM-non 0.46%, HTN-non-adherent/DM-adherent 0.50%, dual non-adherent 1.17%. Other ADRD also showed increased risk from dual non-adherence (PR=1.73, 95% CI: 1.16–2.58, p=0.007). Neither HTN nor DM non-adherence alone reached significance for vascular dementia or AD, suggesting synergistic vascular-metabolic damage. Dual non-adherent individuals exhibited higher CRP (11.23 vs 6.55, p<0.001), LDL (81.9 vs 74.4, p<0.001), HbA1c (7.39 vs 7.19%, p<0.001), total cholesterol (158.7 vs 149.0, p<0.001), ferritin (199.0 vs 151.9, p=0.001), and lower albumin (4.03 vs 4.15, p<0.001) compared to dual adherent participants.

Conclusions: Dual medication non-adherence strongly increased VD risk while having no association with AD, demonstrating pathway specificity for cerebrovascular-mediated neurodegeneration. The accompanying pro-inflammatory biomarker profile (elevated CRP, LDL, ferritin; lower albumin) is consistent with sustained vascular-inflammatory injury, potentially mediated through renin-angiotensin system dysregulation. These findings establish dual medication adherence as a modifiable determinant of dementia subtype-specific risk and identify peripheral biomarker signatures supporting targeted vascular cognitive impairment prevention in metabolically compromised populations.

STUDENT POSTER # 104

ALTERED BASAL FOREBRAIN-CORTICAL CIRCUIT ACTIVATION FOLLOWING SURGICAL MENOPAUSE IN RATS. Belthur M, Doyle RT, Pastor J, Balasubramanian KS, Verpeut J, Bimonte-Nelson H, Newbern J. Arizona State University; Arizona Alzheimer's Consortium.

Background: Changes in attention, memory, and executive function are commonly reported during menopause and may interact with aging-related alterations in neural circuits vulnerable to dementia. However, the neurobiological mechanisms underlying these cognitive changes remain poorly understood, including the contribution of female reproductive organs beyond ovarian hormone loss alone. In prior work, we observed spatial memory impairments in female rats following bilateral ovariectomy (Ovx) or hysterectomy (Hyst). Ovx models further indicate that reduced circulating estrogens are associated with memory impairments and altered gene expression in cognition-related neural systems, including basal forebrain cholinergic neurons (BFCNs), which regulate attention, learning, and memory through projections to the cortex, hippocampus, and amygdala. Here we examined whether surgical menopause in rats alters neuronal composition or patterns of activity dependent protein expression within basal forebrain-cortical circuits.

Methods: In this study, we analyzed neuronal subtype density and expression of FOS, an activity-dependent protein marker, in the basal forebrain and medial prefrontal cortex (mPFC) following hysterectomy or bilateral ovariectomy. Brain sections were processed using immunohistochemistry with antibodies targeting specific neuronal subtype markers and FOS. High-resolution confocal microscopy and digital image analyses were used to assess the effects of Ovx and Hyst on neuronal subtypes implicated in basal forebrain–mPFC circuit function.

Results: We did not detect significant differences in the density of key neuronal subtypes within the basal forebrain or medial prefrontal cortex following Ovx or Hyst. However, both surgical manipulations were associated with changes in the proportion of specific neuronal subtypes co-labeled for FOS. These altered activity patterns coincide with spatial memory deficits previously observed in this model.

Conclusions: These findings suggest that loss of the ovaries or uterus does not substantially alter the number of core neuronal subtypes within BFCN-cortical circuits at the time point examined. Instead, surgical menopause may induce persistent changes in neuronal activation within these circuits. Further research is needed to determine whether these altered activity patterns contribute directly to cognitive symptoms associated with transitional or surgical menopause. A better understanding of these mechanisms may help identify targets for interventions aimed at mitigating menopause-associated cognitive changes.

STUDENT POSTER # 105

PARENTAL DEMENTIA HISTORY AND MATERNAL DEMENTIAL ONSET AGE PREDICT AGE OF AMYLOID ONSET IN PROGENY. Bouchal Shockness SM, Robb WH, Greig EE, Durant A, Castellano T, Zhang M, Seto M, Buckley R, Hohman T, Koran ME. Mayo Clinic – Arizona; Mayo Clinic – Rochester; Mayo Clinic – Florida; Vanderbilt Memory and Alzheimer's Center; Massachusetts General Hospital; Arizona Alzheimer's Consortium.

Background: Though family history of Alzheimer's Disease (AD) or dementia is a strong risk factor for AD, its influence on the timing of early amyloid accumulation in offspring remains unclear. We leveraged amyloid PET and family history data from two large cohorts to determine whether parental family history predicts timing of amyloid positivity in progeny.

Methods: 2,137 participants from A4 and ADNI with at least one positive amyloid PET scan (Centiloid ≥ 20) and classifiable dementia family history data were included (DEM cohort); 1,983 also had classifiable AD family history data (AD cohort). Harmonized amyloid PET, *APOE*, demographic, and family history data were used. Estimated age of amyloid onset (EAOA) was calculated using the Sampled Iterative Local Approximation method. Linear models tested associations between number of affected parents and offspring EAOA. Next, we examined parental age of symptom onset as a continuous predictor of incremental variance in EAOA. Cox proportional hazards models assessed time to amyloid positivity conversion as a function of family history category and parental onset age. All models were adjusted for sex, *APOE* status, and study.

Results: Each additional affected parent was associated with 11.8–13.1 months earlier offspring EAOA (AD: $\beta=-0.982$, $p=0.006$; DEM: $\beta=-1.090$, $p<.001$). In the DEM cohort, each 10-year decrease in maternal age of dementia onset was associated with 12.5 months earlier EAOA ($\beta=0.104$, $p=0.003$). The association between paternal age of dementia onset and EAOA was marginally significant (DEM: $\beta=0.106$, $p=0.062$). In the smaller AD cohort, neither maternal nor paternal age of AD onset was associated with earlier EAOA. Categorical adjusted Cox models confirmed earlier conversion to amyloid positivity across parental history categories in the DEM cohort (both parents DEM+ HR = 1.394, $p < .001$; mother only DEM+ 1.223, $p < .001$; father only DEM+ 1.205, $p = 0.010$). For AD, maternal but neither paternal nor both-parent history predicted earlier conversion to amyloid positivity (HR = 1.172, $p = 0.003$). Continuous adjusted Cox models showed that only earlier maternal dementia onset age predicted accelerated time to offspring amyloid positivity (1.17 HR per 10-yr earlier onset, $p < .001$).

Conclusions: The number of parents with dementia, as well as maternal AD history and maternal dementia symptom onset age, independently predict EAOA in offspring beyond established risk factors. Taken together, our findings suggest that detailed parental history information could help identify individuals at highest risk for earlier conversion to amyloid positivity, with significant implications for timing of screening recommendations, clinical trial enrollment, and therapeutic interventions.

STUDENT POSTER # 106

PTSD, ALLOSTATIC LOAD, & NEURODEGENERATIVE RISK: EVIDENCE FROM THE ALL OF US RESEARCH PROGRAM. Brucato C, Lewis CR, Braden BB, Ofori E. Arizona State University; Arizona Alzheimer's Consortium.

Background: Post-traumatic stress disorder (PTSD) is associated with an increased risk of late-life dementia, yet the biological and behavioral mechanisms underlying this relationship remain poorly understood. Using All of Us Research Program (AoUOP) data, we evaluated whether trauma-based allostatic load (AL) and sleep variability mediate or moderate PTSD's effect on neurodegenerative risk (i.e, mild cognitive impairment [MCI], dementia, or Alzheimer's disease [AD]).

Methods: AoUOP data (CDR v8, March 3, 2026) included 633,548 participants (controls N=628,402, PTSD N=5,146). PTSD, AL (obesity, hypertension, and diabetes scored 0-3), and MCI, dementia, or AD were identified via the Observational Medical Partnership (OMOP). Fitbit sleep data subsample, N=42,844 (controls N=42,347, PTSD N=497). Poisson regression with robust standard errors and linear probability models evaluated associations between PTSD and neurodegenerative outcomes, adjusting for veteran status, age, gender, APOE e4 status, depression, and AL. Mediation by AL examined attenuation of PTSD's effect after adding AL. Moderation by sleep variability was evaluated, and the PTSD and sleep variability interaction term was not significant.

Results: The PTSD cohort was slightly older 59.8 vs 56.6 years, the majority were male 56.5% vs 36%, and 62.1% were veterans. PTSD participants had higher MCI 9.42% vs 0.80% in controls; 2.22% had dementia vs 0.48% in controls. Most PTSD participants with a neurodegenerative diagnosis had PTSD diagnosed first (68%), preceding the neurodegenerative diagnosis by a mean of 2.97 years. After full adjustment, PTSD predicted MCI (PR=2.25, CI 2.04-2.49, $p<0.001$, risk difference = 5.91 points), dementia (PR=1.37, CI 1.12,1.66, $p<.002$), and any neurodegenerative condition (PR=1.99, CI 1.81-2.18, $p<0.001$, risk difference = 5.52 points). AL markers were elevated in PTSD participants by 56.9% for obesity, 65.1% for hypertension, and 22% for diabetes. AL remained significant (beta=0.46-0.61), partially mediating the link to MCI 16.3%, 36.3 dementia, 34,3% AD, & any-neurodegeneration 18.7%. Time to MCI increased with AL burden (AL 0=2.31 years, n= 35; AL3 = 3.37 years, n=84).

Conclusions: PTSD may increase neurodegenerative risk through multiple pathways. AL is significant in PTSD, contributing but not fully explaining PTSD's associations with MCI, dementia, and any neurodegenerative risk. PTSD remained an independent predictor of dementia and MCI. Given the PTSD veteran population, these associations suggest that AL markers could identify individuals benefiting from earlier cognitive screening and closer coordination between psychiatric and primary care.

STUDENT POSTER # 107

MIRNA SIGNATURE-MATCHING FOR THERAPEUTIC DISCOVERY IN NEURO-DEGENERATIVE DISORDERS. Byrne B, Mendoza D, Drake J, Vladimirov V, Schrauwen I. University of Arizona College of Medicine – Phoenix; Arizona Alzheimer's Consortium.

Background: Neurological disorders are the second leading cause of death, encompassing epileptic syndromes, neuropsychiatric diseases, and neurodegenerative diseases such as Alzheimer's, but are targeted by a mere 7% of existing therapeutics. Financial burden, late-stage trial failures, and extensive research timelines have catalyzed drug repurposing as an alternative to overcoming challenges in novel compound discovery. It involves the application of previously FDA-approved therapeutics for new indications, as studies have suggested that a singular drug may be exploited across various diseases and biological systems. One recent example of its utility is the discovery of the multipurpose nature of Vorinostat, an established anticancer drug that reverses the Rett syndrome phenotype in preclinical models while reducing other neuropsychiatric and neurodegenerative disease pathology.

Methods: Our lab develops computational pipelines that leverage omics data to identify new therapeutic applications for neurological disorders. We developed one such pipeline that statistically interrogates mRNA disease signatures against expression profiles of several compounds derived from the SigComLINCS database. This includes FDA-approved therapeutics, pathway modulators, and investigative compounds across approximately 244 cell lines. Potential disease therapeutics resulting from this comparison are those that reflect an opposing transcriptomic signature to the disease signature, reversing the pathogenic mechanism. The aim of this project is to complement and expand this approach by incorporating neuronal miRNAs, which are dysregulated in several neurological diseases, as therapeutic targets of small molecule compounds that have already been assessed for efficacy and safety.

Results: We identified an existing miRNA-seq dataset of human iPSC-derived neurons treated with 1902 compounds, including FDA-approved compounds, inhibitors, active pharmaceutical agents, chemotherapeutic agents, and natural products. We have designed a computational framework for analyzing small RNA data that is focused on miRNA reverse signature matching. The tool is under development and can be used complementary to our mRNA pipeline but will be refined and customized to specifically suit our aim of identifying therapeutic candidates that impact neuronal miRNAs associated with neurological disorders.

Conclusions: Our end-goal is to apply this pipeline to various neurological diseases, including those of aging and neurodegenerative origin, through analysis of publicly available datasets and internally generated data from in-house postmortem brain tissue. This could aid in acceleration of research through broadening the understanding of miRNAs and pathogenic mechanisms implicated in the progression of Alzheimer's and similar diseases while increasing therapeutic options.

STUDENT POSTER # 108

ADVANCED PERFUSION MAGNETIC RESONANCE IMAGING AND PLASMA BIOMARKERS IN ALZHEIMER'S DISEASE. Bues HF, Keeling EG, McElvogue MM, Ott LR, Bakkar N, Stokes AM. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: Cerebrovascular alterations are an emerging area of interest in Alzheimer's Disease (AD) research. Lower cerebral blood flow (CBF) has been observed early in disease, preceding cognitive decline. However, the relative contributions of macrovascular and microvascular dysfunction remain unclear. The goal of this study was to assess CBF in AD on both the macrovascular and microvascular level, and relate this metric to blood proteomics of neurodegeneration, inflammation, and vascular health to investigate the molecular basis for vascular dysfunction as observed via magnetic resonance imaging (MRI).

Methods: MRI data were acquired at 3T (Ingenia, Philips) in 2 participant groups, healthy controls (n=11, 8 F; 70.2±9.9 years) and AD (n=8, 2 F; 76.6±8.3 years). Immediately prior to MRI imaging, cognitive testing was performed, including the Montreal Cognitive Assessment (MoCA), and plasma samples were collected. Dynamic susceptibility contrast (DSC) MR perfusion data were acquired using our spin- and gradient-echo (SAGE) acquisition (5 echoes, 7.7/26/56/74/92 ms) before, during, and after injection of gadolinium-based contrast agent. Perfusion data were processed using in-house bash and MATLAB scripts to generate CBF maps. Plasma samples were run through a targeted proteomics panel for proteins related to neurodegenerative diseases.

Results: MoCA scores are in line with expected results, with healthy controls (25.9±3.1) showing higher performance than AD patients (14.6±6.5). As expected, microvascular CBF was lower than macrovascular CBF in both healthy controls and AD in all regions. A trend of lower CBF was observed in AD vs healthy controls. Blood proteomic analyses revealed higher levels of markers related to neurodegeneration and inflammation in AD. Correlation analyses between imaging metrics and blood analytes are still ongoing.

Conclusions: By separately characterizing macrovascular and microvascular CBF, SAGE may provide a sensitive approach for detecting early vascular alterations associated with aging and neurodegenerative disease. Correlations between CBF and blood analytes will inform which molecular processes relate to broader changes in vascular function.

STUDENT POSTER # 109

DIFFUSION-WEIGHTED PHASE CONTRAST VELOCIMETRY TECHNIQUE FOR CSF FLOW QUANTIFICATION THROUGH THE RAT CEREBRAL AQUEDUCT. Carlson R, Williamson N, Howison C, Komlosh M, Basser P, Hutchinson E. University of Arizona; National Institute of Health; Arizona Alzheimer's Consortium.

Background: The ability to quantify slow neurofluid flow is necessary for the detection and characterization of many neurological conditions. Changes in CSF movement due to pathophysiology, particularly Alzheimer's disease, have been highlighted through the recent description of the glymphatic and meningeal lymphatic systems. The glymphatic system proposes a mechanism of slow, CSF-mediated waste clearance through the brain affected by the accumulation of macromolecules like amyloid-beta. Current MRI imaging methods such as phase contrast MRI measure blood and cerebrospinal fluid (CSF) velocity, sensitive to fast flow on the range of cm/s to mm/s. Slow flow (<1mm/s) is challenging to directly measure in vivo, though diffusion-weighted (DW) imaging approaches show promise.

In this study, we aim to measure velocity in vivo using a DW-MRI velocimetry technique. To test this method, we imaged a tube flow phantom and the rat cerebral aqueduct (CA), an in vivo structure comparable to tube flow. The development of this MRI method will aid in the in vivo characterization CSF neurofluid flow, laying the groundwork to measure slow interstitial glymphatic flow.

Methods: MR images were acquired in a tube flow phantom and in Sprague-Dawley rats (n=7) on a Bruker 7T Biospec 70/20 pre-clinical MRI scanner. Complex DW-MRI signal was acquired with a pulse gradient spin echo sequence of a single slice perpendicular to the flow direction. The 2D image was acquired with an echo planar read out, an echo time of 53 ms, repetition time of 3000 ms, and spatial resolution of 0.175 x 0.2 x 0.8 mm. DW-MRI phase velocimetry is sensitive to the translational motion of water molecules, encoding both diffusion coefficient and coherent velocity in its signal. Velocity maps were calculated in MATLAB from the phase of the complex signal. In vivo, scans were gated on heart rate and respiration rate to minimize the influence of CSF pulsatility on MRI signal.

Results: Laminar velocity profiles were measured in the tube flow phantom, showing a clear linear relationship with expected mean velocity, establishing that DW-MRI phase velocimetry is capable of accurately measuring fluid velocity. Next, methods were translated in vivo. Velocity is measurable in the rat CA and 4th ventricle, however factors including CSF pulsatility make this measurement more challenging. Unidirectional flow was observed in the CA, while bidirectional flow was observed in the 4th ventricle.

Conclusions: Here, we observe and quantify flow in a phantom and in vivo through a DW-MRI technique, though calibration and validation of this method is crucial. The development of tools to characterize CSF flow supports a wide range of neurologic disorder studies in which CSF transport and waste clearance are implicated. As this project progresses, we plan to understand the influence of CSF pulsatility of MRI signal, translate it to slow flow regimes, and implement method in a transgenic Alzheimer's Disease rat model.

STUDENT POSTER # 110

ENHANCING ALZHEIMER'S DISEASE RESEARCH VIA AI. Chen C, Chen K. Brophy College Preparatory; Arizona State University; Banner Alzheimer's Institute; University of Arizona College of Medicine - Phoenix; Arizona Alzheimer's Consortium.

Background: In Alzheimer's disease (AD) research, amyloid positron emission tomography (PET) scan plays an important role in AD diagnosis and assessment. Images generated from amyloid PET scans are used to estimate β-amyloid (Aβ) deposition in the brain. A semi-quantitative analysis of PET images, called Standardized uptake value ratio (SUVR), provides a rough estimation of Aβ load. SUVRs calculated using different reference regions (RR) may result in different estimates. Hypometabolic convergence index (HCI) was introduced as a global measure of AD related hypometabolism.

Methods: In this project, we compare SUVRs obtained using two different RRs, wm and cb, in their relationship to HCI. A large data set obtained from Alzheimer's Disease Neuroimaging Initiative (ADNI) was used. We apply six popular AI/machine learning methods, Partial least square (Pls), Regression tree (Rpart), Elastic network (Glmnet), K nearest neighbors (KNN), Random Forest (RF), Multilayer neural network (NN), and Support vector machine (SVM) to the training data and compare the performance with testing data of each method applied to different models in terms of the way to use SUVRs (neither, either SUVR with reference region wm or cb, and both SUVRs with reference region wm or cb). Each final model is then applied to the corresponding testing dataset to assess its performance based on the three indices: root mean square error (RMSE), r-squared (R2), and mean absolute error (MAE).

Results: For data over all subjects, and data within each diagnostic sub-group, and for each ML approach, a model including mcSUVRwm always performed better than the model including mcSUVRcb in terms of smaller RMSE and MAE values, and larger R2.

Conclusions: Our results show that using SUVR with wm RR performs better than SUVR with cb RR in terms of stronger relationship with HCI. In addition, using both SUVRs together usually performs better than using SUVR with only one of the two RRs. This new finding suggests a novel way to use SUVRs with both RRs in future AD studies.

STUDENT POSTER # 111

HANDEDNESS AND ALZHEIMER'S DISEASE: RESULTS FROM MINDCROWD STUDY. Chen C, Huentelman M, Chen K. Brophy College Preparatory; Translational Genomics Research Institute; University of Arizona College of Medicine - Phoenix; Banner Alzheimer's Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: Handedness is closely related to hemispheric lateralization of brain function and has been associated with differences in cognition and brain activity. Alzheimer's disease (AD) may also involve asymmetric structural and functional brain changes. However, previous studies examining the relationship between handedness and AD have reported inconsistent findings, partly because of limited sample sizes. We examined the association between handedness and self-reported AD using data from the large MindCrowd online cognitive-aging study.

Methods: MindCrowd is a web-based cognitive-aging research platform developed and hosted at TGen and serves as Project 1 of the Precision Aging Network. The current analysis included 154,456 participants aged 50 years and older after excluding participants with missing data and participants from response categories with very small sample sizes. Handedness was classified as right-, left-, or mixed-handedness, with right-handedness as the reference group. Logistic regression models were used to estimate unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Adjusted models included age group, sex, race, ethnicity, education, and smoking status. Age-stratified analyses were also conducted for participants aged 50–59, 60–69, 70–79, and 80 years or older.

Results: Among 154,456 participants, 1,697 reported AD. Right-, left-, and mixed-handed participants accounted for 87.55%, 10.13%, and 2.33% of the sample, respectively. Self-reported AD prevalence was higher among left-handed participants (1.37%) and mixed-handed participants (3.34%) than among right-handed participants (1.01%). In adjusted analyses, both left-handedness and mixed-handedness were associated with greater odds of self-reported AD compared with right-handedness. The adjusted OR was 1.42 for left-handedness (95% CI: 1.23–1.64, p = 2.48 × 10^-6) and 2.08 for mixed-handedness (95% CI: 1.69–2.53, p = 8.47 × 10^-13). Across age-stratified analyses, mixed-handedness consistently showed a stronger association with self-reported AD than left-handedness.

Conclusions: In this large MindCrowd observational sample, non-right-handedness was associated with higher odds of self-reported AD, with the strongest association observed for mixed-handedness. These findings suggest that handedness may provide useful context for studies of individual differences in AD-related cognitive and brain changes. Because AD status was self-reported and the study was observational, future studies using clinically confirmed diagnoses, biomarker data, and more representative samples are needed.

STUDENT POSTER # 112

BRAIN MICROSTRUCTURE QUANTIFICATION IN INDIVIDUALS WITH ASYMPTOMATIC EXTRACRANIAL CAROTID ARTERY DISEASE UTILIZING FIXEL-BASED-ANALYSIS OF DMRI. Chen L, Wiskoski H, Camilo Arias J, Ugonna C, Trouard T, Weinkauf C. University of Arizona; Arizona Alzheimer's Consortium.

Background: Asymptomatic extracranial carotid artery disease (aECAD) is caused by plaque buildup or stenosis in the carotid artery, the main supplier of blood to the brain. aECAD is evaluated clinically for stroke prevention, but has been associated with an increased risk for Alzheimer's Disease and related dementias (ADRD). The mechanisms relating aECAD to poorer cognitive outcomes remain unknown. aECAD-associated changes in cerebral perfusion may cause changes in brain microstructure. Fixel-based analysis (FBA) of diffusion MRI (dMRI) provides a non-invasive way of modeling tissue microstructure. In this study, we utilize FBA to investigate microstructural changes in individuals with aECAD compared to controls.

Methods: 150 adults (mean age =72 yo, std=8) were prospectively stratified by maximum stenosis: No aECAD (<50% stenosis, n=68) and aECAD (≥50% stenosis, n=82). Exclusions included dementia, major depression, stroke/TIA in the past 6 months, neurological disease, or heart failure. Multi-shell dMRI (b=500, 1000, 2000 s/mm^2; 2 mm isotropic; 136 directions) was acquired on a 3T Siemens Skyra. The *MRtrix3* FBA pipeline was used for analysis, which involves response function estimation, fiber orientation distribution (FOD) estimation using constrained spherical harmonic deconvolution (CSD), fixel generation through integration of FOD lobes, and fixel-wise statistics of microstructural integrity metrics: fiber density (FD), fiber cross-section (FC), and fiber density and cross-section (FDC). We evaluated fixel-wise differences in these metrics between No aECAD and aECAD participants.

Results: Differences in fixel metrics were observed between aECAD and no aECAD participants. Clusters of fixels with significant differences in FD (uncorrected $p<.05$) were observed in in the corpus callosum. Fixels of significant difference in FC (uncorrected $p<.05$) were observed in the white matter of the temporal lobe. Significantly different fixels in FDC (uncorrected $p<.05$) were observed in both the corpus callosum and white matter of the temporal lobe. However, after family wise error correction, no fixels of significance remained.

Conclusions: This study demonstrates the use of FBA to assess microstructural changes in individuals with aECAD. While results did not survive multiple comparisons correction, fixel clusters were identified in all 3 parameters suggesting potentially small changes in microstructure. Future work will assess fixel metrics within specific white matter tracts of interest and account for demographic and vascular risk factors. Looking at microstructural changes in white matter tracts may tell us about a specific microstructural integrity metrics and deepen our understanding of how aECAD affects the risk and development of ADRD.

STUDENT POSTER # 113

ARC MRNA EXPRESSION PATTERN IN CA1 HIPPOCAMPAL SUBREGION REVEALS ENSEMBLE STABILITY DIFFERENCES ACROSS AGE AND COGNITION. Chen YJ, Chawla MK, Zempare MA, Khattab S, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

Background: Cognitive function changes with age, yet these age-related alterations have varying effects across individuals. The neural circuit mechanisms underlying this variability remains poorly understood. To address this, we investigated the stability of hippocampal neural ensembles among individuals with differing spatial memory ability across the rodent lifespan from 6-23 months in the male F344 rat. Our study focused on the CA1 subregion of the hippocampus, which receives topographically organized input from the entorhinal cortex. Specifically, distal CA1 receives projections from the lateral entorhinal cortex (LEC), proximal CA1 from the medial entorhinal cortex (MEC), and medial CA1 from both EC regions. These distinct inputs result in functional segregation along the CA1 transverse axis. In this study, catFISH (cellular compartment analysis of temporal activity by fluorescence in situ hybridization) was used to map behavior induced Arc mRNA expression in hippocampal neuronal populations at single-cell resolution. Network stability was assessed by identifying cells activated during two separate behavior sessions. Male Fischer-344 rats from three age groups (6, 15, and 23 months) were classified into high-, average-, and low-performing groups based on their Morris watermaze performance. We hypothesized that both aging and cognitive status would be associated with differential ensemble stability in CA1. Previous results (Chen et al, 2024 SfN abstract) from the middle CA1 region revealed a significant effect of age, with high-performing old rats exhibiting a higher proportion of double-labeled Arc-positive cells than low- or average-performing old rats. This suggests greater network stability in this group. Here we present data obtained from proximal and distal CA1.

Methods: Behaviorally induced Arc mRNA expression was investigated by allowing the rats to explore the same environment twice for 5 minutes each, with a 20-minute rest period in their home cage. To visualize Arc mRNA expression patterns, in situ hybridization (catFISH) was conducted and imaged using a Zeiss LSM 800 confocal microscope. Our behavioral strategy enabled the observation of cells with Arc mRNA expression in the nucleus, cytoplasm, or both compartments, which were subsequently counted using ImageJ software.

Results: Both proximal and distal CA1 subregions exhibited distinct patterns of Arc expression across aging and cognitive performance. In proximal CA1: • No difference in network stability was noted in young rats with low, average, or high cognitive abilities (no difference in Arc+ double-labeled cells). • Consistent with the previous findings in middle CA1 region, old high-performing rats exhibited greater network stability compared to the other high-performing groups (more Arc+ double-labeled cells). In distal CA1: • Consistent with the middle and proximal regions, there is no difference in network stability between young rats with low, average, or high cognitive abilities (no difference in Arc+ double-labeled cells). • Old high-performing rats exhibited greater network stability compared to the other high-performing age groups. Notably, middle-aged rats displayed a puzzling result. One possible explanation can be offered. The middle-aged group has the fewest rats counted to date, and this low "n" may explain the unexpected decline in Arc positive double labelled cells in the high-performing group.

Conclusions: There are two major findings: (1) Within the high-performing rats of all ages, only the high-performing old rats showed a higher proportion of double-labeled Arc-positive cells (marginally significant) than the young and middle-aged groups. (2) When comparing across different performance levels, only the high-performing old rats showed a marginally significant effect of performance level on double labeled cells in the proximal region. Data collection is still ongoing, with ~85% of the tissue samples examined in a blinded procedure.

STUDENT POSTER # 114

LEXICAL FILLERS, APOLIPOPROTEIN E4 STATUS, AND EPISODIC SPECIFICITY IN PAST AND FUTURE AUTOBIOGRAPHICAL THINKING. Cohen D, Klus J, Espinoza M, Daelemans R, Pfeifer V, Andrews-Hanna J, Mehl M, Grilli M. University of Arizona; University of Missouri - Kansas City; Arizona Alzheimer's Consortium.

Background: Little is known about what the use of lexical fillers (e.g. "like", "I mean", "you know", "well") signals about a speaker's underlying cognitive functioning. A few studies investigating lexical fillers suggest that they may be used to express that speakers are experiencing cognitive challenges, need to rephrase, or are not fully committed to what they say. Given age-related changes in cognitive functioning, the present preregistered study explored whether lexical fillers usage reflects risk for age-related cognitive decline independently and in relation to lower episodic specificity on autobiographical narratives. We investigated lexical filler differences in apolipoprotein E4 (APOE4) carriers and noncarriers during autobiographical memory and future thinking tasks. We also examined the correlation between episodic specificity and lexical filler usage and investigated whether this correlation was stronger in the future or past thinking task. Notably, lexical fillers can maintain surface-level fluency despite cognitive load, and future thinking trials significantly increase difficulty for episodic detail generation.

Methods: The sample consists of an archival dataset with 82 cognitively normal older adults (ages 60-80), with 39 Apolipoprotein e4 (APOE4) carriers and 43 non-carrier matched controls. This study used an adapted version of a past and future thinking narrative task with participants asked to retrieve 5 memories and imagine 5 future events in as much episodic detail as possible. Research assistants first tagged lexical fillers (e.g. "like", "I mean", "you know", "well") based on context, and then lexical fillers were identified using the "Fillers" category in Linguistic Inquiry and Word Count-22 (LIWC-22). In a 2x2 ANOVA, we included APOE status (APOE4 carrier versus noncarrier) and task (future thinking versus memory) as independent variables and percentage of lexical fillers, relative to total words, as the dependent variable. We also conducted Spearman correlations to investigate the relationship between episodic specificity and percentage of lexical fillers, first with the memory and future thinking tasks combined and separated in a follow-up.

Results: The main effect of APOE4 status on lexical fillers was not significant, $F = .006$, $p = .94$, nor was the main effect of task (memory versus future thinking) on lexical fillers significant, $F = 1.32$, $p = .25$. However, a higher percentage of lexical fillers in the memory and future thinking tasks combined was correlated with lower average episodic specificity in the two tasks, $\rho = -.25$, $p = .02$. When lexical fillers were analyzed separately by task, a higher percentage of lexical fillers was significantly correlated with lower episodic specificity on the memory task, $\rho = -.23$, $p = .04$, and on the future thinking task, $\rho = -.33$, $p = .002$. A formal comparison indicated that these two correlations did not differ significantly from each other, 95% CI for the difference = [–0.09, 0.29].

Conclusions: Lexical filler usage may not differ by APOE4 status or future versus past autobiographical thinking. However, using lexical fillers may indicate that a speaker is having difficulty constructing autobiographical events episodically, as instructed by the tasks in this study.

STUDENT POSTER # 115

INVESTIGATING ACVR1C LOCALIZATION TO THE ENDOSOMAL SYSTEM DURING MEMORY CONSOLIDATION. Connell B, Wright E, Keiser AA. Arizona State University; Arizona Alzheimer's Consortium.

Background: Aging is associated with a gradual decline in cognitive function and is the greatest risk factor for the development of neurodegenerative disorders, including Alzheimer's disease (AD). Emerging evidence suggests that endosomal trafficking becomes dysregulated during aging, contributing to altered cellular signaling and impaired neuronal function. Because endosomal trafficking regulates the internalization, recycling, and signaling of transmembrane receptors, disruptions in these pathways may contribute to altered cellular signaling and cognitive impairment in aging. Activin A Receptor Type 1C (ACVR1C) is a transmembrane receptor within the transforming growth factor-beta (TGF-beta) superfamily signaling pathway, mediated by endosomal trafficking, that has emerged as a bidirectional regulator of hippocampal-dependent memory and synaptic plasticity. Acvr1c is significantly reduced in the hippocampus of aging mice and humans and Acvr1c overexpression in the mouse dorsal hippocampus rescues cognitive decline. Despite ACVR1C's implicated role in cognitive function, very little is known about its intracellular signaling and how it is regulated within endosomal compartments. This gap in our knowledge of ACVR1C signaling in memory consolidation limits the evaluation of this TGF-β receptor as a therapeutic target for cognitive dysfunction.
Hypothesis: Endosomal trafficking critically regulates ACVR1C signaling during hippocampus-dependent memory consolidation.

Methods: To investigate the role of ACVR1C trafficking during memory consolidation, 5-month-old wild-type mice and 18-month-old wild-type mice will be trained for 10 minutes in the Object Location Memory (OLM) paradigm. Following training, the dorsal hippocampus will be collected during the memory consolidation window, 1-hour post-training. Home-cage mice will serve as controls (OLM: n = 5 mice/sex/age; home cage: n = 5 mice/sex/age). Hippocampal tissue will be processed for immunofluorescent staining to assess ACVR1C localization within the endosomal pathway using established markers of early endosomes (Rab5), late endosomes (Rab7), recycling endosomes (Rab11), and lysosomes (LAMP1/Cathepsin D). Confocal imaging will be performed on the Nikon Eclipse A1R/Ti2 confocal microscope, and colocalization analyses will be conducted in ImageJ to quantify ACVR1C trafficking during memory formation.

Results: We expect to observe ACVR1C trafficking patterns that support the hypothesis that ACVR1C is regulated through endosomal trafficking pathways. Additionally, we anticipate seeing age-related disruptions in ACVR1C trafficking dynamics such as Rab5 (early endosome) overactivation and enlargement, reduced localization within late endosomes and impaired recycling within aging.

Conclusions: Characterizing endosomal trafficking of ACVR1C under normal, healthy conditions and in aging is crucial for understanding its role in memory consolidation and how age-related alterations may contribute to its dysfunction. Defining ACVR1C's signaling pathway will enable future studies to investigate AD mouse models to determine how endosomal dysfunction impacts ACVR1C signaling within the context of Alzheimer's mechanisms.

STUDENT POSTER # 116

CLONING A PINE-TREE PE-PEGRNA(DT)-SGRNA(DT) VECTOR FOR MODELING THE BIN1 K358R MUTATION. Crawford D, Leyasi S, Brafman D. Arizona State University; Arizona Alzheimer's Consortium.

Background: The BIN1 gene variants are implicated as one of the strongest genetic risk factors for Alzheimer's disease (AD). Specifically, BIN1 is linked to disease-related tau pathology, and BIN1 K358R is associated with AD in populations of Caucasian and Caribbean Hispanic descent. However, BIN1 variant differences in isoform-specific interaction with tau pathology and its role in AD pathophysiology are incompletely understood. The goal of this project was to gain a deeper understanding of Alzheimer's disease in the context of the BIN1 K358R variant. The objective was to construct a prime-induced nucleotide engineering using a transient reporter for editing enrichment (PINE-TREE) plasmid as a route to developing a clonal isogenic line of human-induced pluripotent stem cells (hiPSC) of the BIN1 K358R mutation. The PINE-TREE editing system enables efficient generation of hiPSC lines without deleterious double-strand breaks, indels, or off-target modifications present in other genomic editing techniques.

Methods: The plasmid for the BIN1 K358R target was constructed using a method previously established in Frisch et al. (2026). The pegRNA(BIN1-K358R) and nicking sgRNA(BIN1-K358R) constructs were individually cloned and ligated into the pHSG1C3 plasmid (Addgene #164423). These intermediate vectors added a U6 promoter upstream of the inserts. Ligation products were transformed into NEB® 10-beta Electrocompetent E. coli, and clones were screened via Sanger sequencing. Successful pegRNA(BIN1-K358R) and sgRNA(BIN1-K358R) intermediates were multiplexed into the PE-pegRNA(BG)-sgRNA(BG) plasmid (Addgene #232727), generating the final dual target plasmid construct. This was achieved through PCR amplification of the pegRNA(BIN1-K358R) and sgRNA(BIN1-K358R) intermediates to add HindIII and SapI sites, restriction enzyme digest of the inserts and PE-pegRNA(BG)-sgRNA(BG) vector, a multiplex ligation, and a similar transformation and screening process as the intermediate cloning.

Results: The final PINE-TREE plasmid product was verified via Sanger sequencing, showing that the pegRNA and sgRNA inserts were successfully multiplexed with all four U6 promoters. Thus, this validated PINE-TREE plasmid can be used for the future generation of a clonal isogenic line of hiPSCs of the BIN1 K358R mutation.

Conclusions: This plasmid will be utilized to develop a clonal isogenic hiPSC line to model the BIN1 K358R Alzheimer's disease-associated genetic risk variant, allowing us to observe differences within these cell lines and wild-type lines. This project enables the continuation of the ongoing project to deepen the understanding of how genetic variation within BIN1 coding regions increases the risk of developing AD in the context of the BIN1 K358R mutation.

STUDENT POSTER # 117

DIFFUSION-WEIGHTED RADIAL TURBO SPIN ECHO FOR HIGH-RESOLUTION DIFFUSION-WEIGHTED IMAGING AT 0.55T. Curley B, Ahanonu E, Toner B, Goerke U, Chen NK, Altbach M, Trouard TP, Bilgin A. University of Arizona; Siemens Healthineers; Arizona Alzheimer's Consortium.

Background: Diffusion-weighted MRI is most commonly carried out using single-shot echo-planar imaging (SSEPI). However, SSEPI is limited by geometric distortion, susceptibility-related signal loss, particularly at air-tissue interfaces, and constraints on spatial resolution. Diffusion-weighted radial turbo spin-echo (DIFRAD-TSE) imaging provides an alternative strategy by combining diffusion preparation with a multi-shot radial-TSE readout, enabling spin-echo-based diffusion imaging with reduced sensitivity to shot-to-shot motion-induced errors. Low-field MRI at 0.55T is well suited for revisiting this approach because reduced susceptibility effects may complement the distortion-resistant radial spin-echo acquisition, while the lower intrinsic SNR creates a need for efficient and robust diffusion-weighted imaging strategies. In this work, we implemented a DIFRAD-TSE sequence on a Siemens Free.Max 0.55T scanner and evaluated its capability to enable high-resolution diffusion-weighted imaging.

Methods: The DIFRAD-TSE pulse sequence was implemented by modifying an existing radial turbo spin-echo (RAD-TSE) sequence to include a spin-echo preparation period prior to the radial-TSE readout. In the DIFRAD-TSE experiments, a TR of 1500 ms, an echo-spacing of 11 ms, and a preparatory time of 90 ms were employed. The sequence was run with b values of 0, 74, 144, 294, 497, 752, and 952 s/mm^2 in the x, y, and z axes independently. SSEPI comparisons utilized a commercial sequence (TR = 4000 ms, TE = 115 ms) with b-values of 150, 400, 600, 750, and 900 s/mm^2. DIFRAD-TSE and SSEPI images were acquired of a NIST/QIBA Diffusion Phantom. Apparent diffusion coefficient (ADC) maps were generated for each direction of diffusion. ADC values were calculated and compared to those provided by the phantom manufacturer.

Results: DIFRAD-TSE showed less image distortion due to magnetic field inhomogeneity compared to SSEPI at all b-values measured. Both sequences demonstrated exponential signal decay with b-value as expected. With diffusion in the X direction, the R^2 values from the DIFRAD-TSE and SSEPI sequences were 0.986 and 0.996, respectively. In the Y direction, the R^2 values of the DIFRAD-TSE and SSEPI sequences were 0.567 and 0.99, respectively. In the Z direction, the R^2 values of the DIFRAD-TSE and SSEPI sequences were 0.989, and 0.999, respectively. Eddy currents likely caused discrepancy in the DIFRAD-TSE Y direction as the SSEPI displayed lower average signal values in the Y direction.

Conclusions: This work introduces a DIFRAD-TSE MRI pulse sequence that enables multi-shot diffusion MRI to be carried out on a low-field, low gradient strength MRI scanner. DIFRAD-TSE images showed less distortion due to magnetic field inhomogeneities compared to SSEPI. The results are promising for enhancing diagnostic capabilities for diseases in the brain and making these capabilities more affordable and accessible.

STUDENT POSTER # 118

ASSOCIATION BETWEEN BRAIN AGE GAP AND WHITE MATTER HYPERINTENSITY BURDEN IN PRECISION AGING NETWORK. Das D, Karakay D, Ugonna CP, Matijevic S, Chen NK, Trouard TP, Ryan L, Altbach MI, Bilgin A. University of Arizona; Arizona Alzheimer's Consortium.

Background: Brain Age Gap (BAG) is an MRI-derived biomarker that reflects patterns of brain structural decline associated with aging. White matter hyperintensities (WMHs), which appear as regions of increased signal intensity on fluid-attenuated inversion recovery (FLAIR) images, indicate alterations to cerebral white matter that is predominantly presumed to be of vascular origin. We investigated whether WMH burden is independently associated with accelerated brain aging in the Precision Aging Network (PAN) cohort.

Methods: Data were obtained from 567 cognitively normal older adults enrolled in PAN (mean age = 63.9 ± 7.7 years). Brain age was estimated from T1-weighted MRI using three machine learning models: the USC Brain Age model, BrainAgeR, and PyMent. BAG was calculated as predicted age minus chronological age. WMH burden was quantified from T1-weighted and FLAIR images using three established segmentation methods (LST-AI, UniSelf, and SHiVAi) and expressed as log(WMH volume + 1). Participants with missing data were excluded from statistical analyses, resulting in a final analytic sample of 543 participants. Fully adjusted analyses included chronological age, sex, imaging site, and total intracranial volume (TIV) as covariates. TIV was scaled by 10^6 to improve coefficient interpretability, and site and sex were modeled as categorical variables.

Results: WMH burden was significantly associated with BAG across all three brain age models and all WMH segmentation methods. After adjustment for chronological age, sex, imaging site, and TIV, significant associations were observed across all brain age models ($r = 0.159–0.294$, all $p < 0.001$). The strongest association was observed between PyMent BAG and SHiVAi derived WMH burden ($r = 0.294$). Multivariable linear regression analyses confirmed these findings ($\beta = 0.564–1.111$, all $p < 0.001$). Associations were consistent across WMH segmentation methods, indicating a robust relationship between greater WMH burden and accelerated brain aging.

Conclusions: Greater WMH burden was associated with higher BAG independent of chronological age sex, or imaging site in PAN cohort. These findings were robust across multiple automated machine learning frameworks for both brain age estimation and WMH segmentation, underscoring the utility of computational pipelines in quantifying neuroimaging biomarkers. The consistency of results across diverse algorithmic approaches suggests that WMH burden may serve as a reliable indicator of accelerated brain aging. Further longitudinal and pathophysiological investigations are warranted to clarify the clinical and mechanistic implications of this association.

STUDENT POSTER # 119

PERCEIVED STRESS AND EPISODIC MEMORY: INVESTIGATING THE MODERATING EFFECT OF PHYSICAL ACTIVITY AMONG HISPANIC AND NON-HISPANIC WHITE MIDDLE AGED TO OLDER ADULTS. Davis M, Guareña L, Ryan L. University of Arizona; The Precision Aging Network; The National Institute of Health-National Institute on Aging; The National Science Foundation; Arizona Alzheimer's Consortium.

Background: The present study examined the relationship between perceived stress and episodic memory performance, as well as the moderating role of physical activity (PA), with a focus on potential differences between Hispanic/Latino and non-Hispanic White (NHW) adults.

Methods: Participants included 314 middle-aged to older adults (241 NHW, 73 Hispanic Latino) from the Precision Aging Network. Perceived stress was assessed using the Perceived Stress Scale (PSS), physical activity using the Quick Physical Activity Rating (QPAR), and episodic memory using an online paired associates learning (PAL) task. Multiple linear regression models tested main and interaction effects of perceived stress and physical activity on PAL performance. To further evaluate the robustness of findings and reduce demographic imbalance across ethnic groups, propensity score matching (PSM) analyses were conducted as sensitivity analyses (72 NHW, 72 Hispanic/Latino).

Results: In the primary sample linear regression model, perceived stress and physical activity were negatively correlated ($r = -0.17$, $p < .01$); however, neither variable was significantly associated with episodic memory performance. Physical activity did not moderate the relationship between perceived stress and PAL performance, and this effect did not differ by ethnicity. In the full sample, Hispanic Latino participants reported higher perceived stress and lower physical activity than NHW participants. Following age, sex, and education matching, Hispanic/Latino and NHW participants no longer differed in perceived stress or physical activity. Education emerged as the most consistent predictor of episodic memory performance across both the primary sample and the matched subsample.

Conclusions: Our findings do not support an association between perceived stress and episodic memory or any moderating role of physical activity in this relationship. Results suggest that demographic factors, particularly education, may play a more prominent role in cognitive outcomes than psychosocial or lifestyle variables in this sample. Future research should employ longitudinal designs and more precise measures of stress and physical activity to better understand these relationships across diverse populations.

STUDENT POSTER # 120

TRANSCRIPTIONAL PROFILING OF THE RELAXIN-3/RXFP3 SYSTEM IN ALZHEIMER'S DISEASE AND ANXIETY. De Louise M, Fermaint M, Valenzuela I, Fang F, Gao H, Luthra M, Intorcia A, Serrano GE, Beach TG, Gundlach A L 5, Schrauwen I, De Ávila C. University of Arizona College of Medicine - Phoenix; Indiana University School of Medicine; Banner Sun Health Research Institute; The Florey Institute of Neuroscience And Mental Health; The University of Melbourne; Arizona Alzheimer's Consortium.

Background: Anxiety disorders are among the most prevalent neuropsychiatric conditions and are highly represented in Alzheimer's disease (AD), affecting up to 40 percent of patients and frequently emerging during prodromal stages such as mild cognitive impairment. Although anxiety is increasingly recognized as a clinically relevant feature of AD, the neurobiological substrates underlying this association remain poorly defined. The pontine nucleus incertus (NI) is a brainstem nucleus that innervates limbic and cortical regions involved in anxiety and cognition, including the amygdala (AMY), hippocampus (HIP), and prefrontal cortex (PFC). Preclinical studies indicate that NI-derived relaxin-3 (RLN3) signaling through the inhibitory receptor RXFP3 modulates arousal, stress responsivity, anxiety-like behaviors, and memory, and that RXFP3 activation is associated with anxiolytic effects. Despite these observations, the molecular organization and transcriptional landscape of the human NI—particularly in the context of AD and anxiety—remain largely unexplored. Emerging transcriptomic evidence suggests that NI RLN3-positive neurons may exhibit distinct gene expression profiles in AD, highlighting this region as a candidate substrate for anxiety-related vulnerability beyond traditional cortico-hippocampal circuits.

Methods: Fresh-frozen postmortem human brain tissue (postmortem interval less than or equal to 3 h) will be obtained from the Banner Brain and Body Donation Program (Sun City, AZ, USA) from age- and sex-matched AD and non-demented control subjects (N equal 6–8 per group). Bulk RNA sequencing will be performed on microdissected NI tissue and on NI projection targets (AMY, HIP, and PFC). Bulk RNA sequencing and computational deconvolution approaches will be used to characterize transcriptional profiles of NI cell populations, including RLN3-expressing neurons. In addition, 10x Genomics Visium Spatial Transcriptomics will be conducted on one formalin-fixed, paraffin-embedded NI slice from a non-demented control and one NI slice from an AD patient with documented anxiety to preserve anatomical context and spatial gene expression patterns. Statistical analyses will include linear regression to examine associations between NI-related transcripts and anxiety and cognitive measures, and multivariable logistic regression models including age and sex as covariates.

Results: This study is expected to generate the first integrated bulk and spatial transcriptomic map of the human NI in aging and AD. We anticipate identifying transcriptional differences in NI neurons, including RLN3-expressing populations, between AD and non-demented cases, as well as spatially resolved gene expression features within the NI that may differ by disease and anxiety status. Bulk RNA-seq of NI projection targets is expected to reveal complementary transcriptional patterns consistent with altered NI-related signaling networks. Together, these datasets are expected to provide a foundational molecular and spatial framework for understanding how NI-associated circuits may be altered in AD with anxiety, while generating openly shareable transcriptomic resources for the scientific community.

Conclusions: By combining bulk and spatial transcriptomics, this work will advance characterization of a largely understudied human brainstem nucleus implicated in anxiety and cognition. The resulting data are expected to expand current neurobiological models of anxiety in AD beyond canonical forebrain regions and inform future hypothesis-driven studies of stress- and anxiety-related vulnerability in neurodegenerative disease.

STUDENT POSTER # 121

BACKGROUND SUPPRESSION WITH SIMULTANEOUS CHEMICAL SHIFT ARTIFACT REDUCTION IN ARTERIAL SPIN LABELING. Dolby AJ, Sonderer CM, Han S, Chen NK. The University of Arizona; Arizona Alzheimer's Consortium.

Background: Chemical shift artifacts from fat in echo planar sequences are difficult to suppress in arterial spin labeling (ASL) imaging without negatively impacting the label signal. The goal of this work is to suppress these artifacts by creating an angular dependency on the complex-value fat, brain, and ASL signals that allows for suppression of fat signals. To accomplish this, we created a custom pseudo-continuous ASL (pCASL) sequence using two different background suppression (BS) timings in one human subject.

Methods: Images were collected from one healthy volunteer on a 3T MR scanner (Cima.X, Siemens, Erlangen, Germany) using a 64-channel receive-only head-coil. A pCASL sequence was created using Pulseq in MATLAB. Two conditions, A (0.369s, 1.047s, 2.204s, and 2.767s) and B (0.510s, 1.577s, 2.203s, and 2.845s) were created through different BS timings and ten label-control pairs were collected for each condition.Complex-value label and control images were averaged independently for each condition, with one condition scaled prior to subtraction across conditions. Resulting complex-value label-control pairs were then pair-wise subtracted to yield perfusion images.

Results: The combination of the conditions, A and B, after scaling allowed for fat tissue suppression while retaining the ASL signal when performing complex-value processing prior to magnitude reconstruction. Standard magnitude subtraction or complex-value processing without image scaling retained chemical-shift artifacts in the label and control images.

Conclusions: We demonstrated that chemical shift artifacts from fat-shifted signals can be suppressed without substantially impacting the ASL signal by varying the BS timings between acquisitions and performing complex-value processing and scaling prior to pair-wise subtraction.

STUDENT POSTER # 122

BRIDGING RESTORATION AND BIOMARKER DISCOVERY: A COMPREHENSIVE FUNDUS IMAGE ENHANCEMENT BENCHMARK FOR RETINAL-BASED ALZHEIMER'S DISEASE DETECTION. Dong X, Zhu W, Chen X, Wang H, Li X, Xiong Y, Dumitrascu O, Wang Y. Arizona State University; Clemson University; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Color fundus photography (CFP) can track Alzheimer's Disease (AD) progression via non-invasive retinal biomarkers, but its diagnostic utility is severely limited by imaging artifacts, defocus, and ocular opacities. While unsupervised generative models can enhance these images without paired data, standard metrics like PSNR and SSIM rely on synthetic noise and fail to measure vital clinical features like vascular morphology consistency. To solve this, we introduce EyeBench-V2, a clinical-alignment benchmark designed to evaluate how effectively fundus enhancement models preserve critical diagnostic markers for AD screening.

Methods: EyeBench-V2 establishes a unified, dual evaluation framework covering both Full-Reference (synthetic noise) and No-Reference (real-world clinical noise) conditions to benchmark fundus image enhancement approaches across five paired baselines (such as SCR-Net, GFE-Net, and RFormer) and eight unpaired generative baselines (such as CycleGAN, OTEGAN, TPOT, and CUNSB-RFIE). Beyond conventional pixel-level metrics, the pipeline routes enhanced outputs through target downstream tasks to measure feature preservation, evaluating retinal microvasculature networks using a vanilla U-Net trained on the DRIVE dataset to quantify vascular topology as a critical proxy for cerebral capillary alterations in AD. Furthermore, diagnostic and semantic feature stability is evaluated through an NN-MobileNet grading model and Fréchet Inception Distance (FID) computations utilizing the Retfound and Ret-Clip foundation models. Finally, real-world clinical applicability is measured via an expert-guided manual protocol where retinal specialists quantitatively score models using Background Preserving Ratio (BPR), Lesion Preserving Ratio (LPR), and Structure Preserving Ratio (SPR) metrics.

Results: The evaluation shows a distinct divergence between pixel-level optimization and clinical utility, where paired approaches achieved high algorithmic performance under Full-Reference conditions due to strict pixel supervision but remain translationally limited by the scarcity of paired real-world medical data. Among the unpaired approaches, topology-aware regularization frameworks (TPOT) led performance in structural and microvascular preservation, achieving top metrics in vessel structural preservation with an AUC of 0.9191. Under real-world No-Reference testing, optimal transport methods utilizing structural losses (OTEGAN) and bidirectional frameworks (CycleGAN) yielded superior downstream grading accuracy up to 0.7588 and robust latent feature alignment, although cycle-consistency objectives occasionally altered fine structural details. Expert manual scoring confirmed a strong, positive Spearman correlation with the multi-dimensional benchmark scores, while simultaneously revealing a critical clinical trade-off: over-emphasizing noise reduction frequently smoothed out fine structures, while over-regularizing structure preservation left residual artifacts.

Conclusions: EyeBench-V2 successfully transitions retinal fundus enhancement from basic algorithmic denoising toward clinically validated biomarker preservation, demonstrating that the integration of clinically informed structural priors, such as topology-aware and perceptual loss constraints, is imperative for generative models to effectively preserve diagnostic features. By pinpointing the performance limits and trade-offs of current GAN and SDE diffusion-based methods in real-world noise settings, this comprehensive benchmark provides an objective validation framework. Ultimately, this work offers actionable technical insights to guide the development of next-generation enhancement models capable of supporting reliable, automated retinal-based screening for Alzheimer's disease

STUDENT POSTER # 123

VESSEL-AWARE OPTIMAL TRANSPORT FOR RETINAL FUNDUS ENHANCEMENT: PRESERVING MICROVASCULAR BIOMARKERS FOR NON-INVASIVE ALZHEIMER'S DISEASE DETECTION. Dong X, Zhu W, Xiong Y, Chen X, Wang H, Li X, Dumitrascu O, Wang Y. Arizona State University; Clemson University; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Retinal color fundus photography (CFP) is a crucial non-invasive window into cerebral health, where microvascular changes mirror neurodegenerative conditions like Alzheimer's disease (AD). However, clinical CFP quality is routinely degraded by illumination, blur, and focus errors. While existing unpaired generative enhancement models mitigate these artifacts, they are highly prone to mode collapse, unstable training, and artificial distortions that fragment global vascular connectivity or create fake vessel branches. These structural modifications alter essential diagnostic features, directly compromising downstream biomarker tracking required for reliable Alzheimer's identification.

Methods: To address these limitations, we propose Vessel-Aware Optimal Transport (VAOT), an unpaired fundus enhancement framework utilizing a two-phase learning objective. First, it minimizes a Monge optimal transport (OT) objective within an adversarial scheme to achieve stable distribution transformations without the high computational overhead of bidirectional mapping. Second, it enforces structure preservation via two multi-scale regularizers: the Skeleton-Guided Global Morphology Alignment (SGA) module uses a differentiable soft-skeletonization process to extract vessel centerlines and penalize structural gaps, while the Endpoint-Based Vascular Integrity Preservation (EVP) module uses neighborhood convolution counting to isolate local termini and apply an SSIM-based local window loss to stabilize subtle, peripheral endpoints.

Results: Evaluated on public benchmarks, VAOT achieves state-of-the-art unpaired enhancement scores on the EyeQ dataset with an SSIM of 0.9433 and a PSNR of 25.253 dB, showing robust cross-dataset generalization on IDRID and DRIVE. Downstream microvascular assessments via automated vessel segmentation underscore VAOT's structural reliability, earning the highest Area Under the ROC Curve (AUC = 0.9184), Precision-Recall curve (PR = 0.7742), and F1-score (0.6966) among all evaluated unpaired models. Qualitative and ablation testing confirm that while alternative translation networks produce fragmented loops or spurious vessels, VAOT faithfully repairs vessel continuity and preserves subtle diagnostic features by combining global and local constraints.

Conclusions: VAOT introduces a novel paradigm in retinal fundus enhancement by effectively coupling optimal transport learning with dual-scale vascular regularizers. By leveraging differentiable soft skeletons and endpoint-centered spatial window anchors, the framework uniquely mitigates acquisition noise while preventing clinically detrimental geometric deformations. This capacity to precisely preserve global structural connectivity and local branch endpoints is highly significant for medical computer vision. Crucially, safeguarding retinal microvascular morphology enables the trustworthy tracking of subtle diagnostic features. This advancement paves the way for reliable, non-invasive screening pipelines that leverage retinal fundus photography to detect and monitor neurodegenerative diseases such as Alzheimer's, ensuring that critical microvascular biomarkers remain uncorrupted during automated image enhancement.

STUDENT POSTER # 124

STEREOTYPED MOVEMENTS IMPROVE TIME ESTIMATION IN THE TGF344-AD RAT MODEL OF ALZHEIMER'S DISEASE AND IN HEALTHY RATS. Dougherty R, Pederson V, Mazurik G, Lovato I, Joshi R, Maillard S, Roemer G, Driscoll A, Bartlett MJ, Cowen SL. University of Arizona; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is associated with robust deficits in time perception including distortions in the ability to track the passage of time at the milliseconds, seconds, and minutes scale. Despite this, the fundamental mechanisms underlying impaired time perception in AD remain unclear. Prior research has shown that both humans and multiple animal species make use of external and self-generated movements (e.g., tapping, vocalizations, grooming) to help estimate time intervals, but whether differences in self-generated movement may underly AD-induced impairments in interval timing has yet to be investigated. We investigated whether TgF344-AD rats, a rat AD model which exhibits key pathological features such as amyloid-beta plaques and neurofibrillary tangles, recapitulates AD-associated deficits in time estimation, and whether such deficits may be due to decreased usage of stereotyped movement routines during interval timing compared to healthy wildtype (WT) controls.

Methods: Rats (AD-Male: N = 11, WT-Male: N = 6, AD-Female: N = 9, WT-Female: N = 7; mean age = 14.22 ± 1.52 mo.) were trained in a negative reinforcement-based time estimation task requiring them to involuntarily walk on a treadmill and wait for 5, 7.5, or 10 s before nose-poking to stop the treadmill. Nose-pokes before the specified interval were penalized by increasing the treadmill speed and length of the trial, requiring rats to estimate elapsed time to withhold responding during the delay. Forward/backward movement trajectories on the treadmill were tracked to assess the use of stereotyped movement routines during time estimation.

Results: Contrary to our hypothesis, we found that AD and WT rats showed similar time estimation accuracy and precision. However, across groups, greater stereotypy in movement trajectory was strongly associated with increased timing accuracy – indicating that movement-based strategies likely played an important role in time estimation in both AD and WT rats.

Conclusions: These findings suggest that in environments which facilitate incorporating external and self-generated movements into a repetitive sequence, time estimation may be improved through development of procedural strategies. Furthermore, as basal ganglia circuitry critical to the learning and execution of procedural motor behaviors remains largely preserved during the early stages of AD, it is possible that time estimation may be less impacted in environments favorable to the development of procedural strategies than in those affording fewer such cues. Future directions include testing whether TgF344-AD rats can flexibly adapt stereotyped movement routines to estimate multiple lengths of time in a context-dependent manner and measuring hippocampal neural ensemble activity during time estimation.

STUDENT POSTER # 125

THE LINK BETWEEN PERIODONTAL DISEASE AND NEURODEGENERATION: A META-ANALYSIS OF ASSOCIATION AND THERAPY STUDIES. Dumitrascu C, Criste E, Kumar G. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: The association between periodontal disease and neurodegenerative disorders has been examined in the scientific literature, although the results have been inconsistent. Existing studies provide mixed evidence regarding the link between periodontitis and both Alzheimer's disease (AD) and Parkinson's disease (PD). Similarly, the effects of various periodontal treatments on the risk of developing AD and PD remain uncertain. In this study, we performed a systematic review and meta-analysis of research investigating (1) the risk of neurodegenerative diseases among individuals with periodontal disease and (2) the impact of periodontal interventions on neurodegeneration. The primary aim was to determine whether periodontal disease represents a modifiable risk factor for AD and PD.

Methods: We adhered to the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines and the PRISMA framework. A comprehensive search strategy was applied across three databases (PubMed, Cochrane, and Embase) to identify studies published between January 2000 and January 2026 that reported either (1) the strength of the association between periodontal disease and cognitive disorders or (2) the impact of periodontal treatment on cognitive outcomes. Two independent reviewers conducted study screening (by titles and abstracts, followed by full-text review), data extraction, and quality assessment using the Newcastle–Ottawa Scale for cohort and case-control studies and the Cochrane Risk of Bias Tool (RoB 2) for randomized controlled trials. To estimate associations, we applied the DerSimonian and Laird random-effects model. Results were presented as risk ratios or hazard ratios with 95% confidence intervals, and forest plots were generated. Heterogeneity was assessed using the I^2 statistic (Cochran's Q test), with a p-value

Results: After removing duplicates, we screened 1,304 titles and abstracts and 325 full-text articles. 97 studies were included in the qualitative synthesis (43 AD, 27 PD, 22 unspecified cognitive impairment/dementia, and 5 periodontal treatment trials). A quantitative synthesis was performed to assess the association between periodontal disease and AD (3 studies; RR 1.78, 95% CI 1.32–2.69, p=0.03, I^2=50) and PD (5 studies; HR 1.19, 95% CI 0.78–2.05, p=0.23, I^2=90). Due to limited quantitative data, and heterogeneity of the therapeutic approaches and outcome measures, the effects of periodontal treatment were evaluated using qualitative synthesis only.

Conclusions: Our meta-analysis identified a significant association between periodontal disease and AD, but not PD. Current evidence is insufficient to determine whether periodontal treatment can prevent neurodegeneration related to AD or PD or delay disease progression. Future randomized controlled trials, incorporating specific periodontal therapeutic approaches, are needed to assess the overall impact of periodontal therapy on cognitive function and the risk of neurodegeneration.

STUDENT POSTER # 126

AN EXAMINATION OF PATHOLOGY DRIVEN BY TWO HUMAN TAU MUTATIONS ON BASAL FOREBRAIN CIRCUITS AND ANXIETY-LIKE BEHAVIOR IN DOWN SYNDROME TS65DN MICE. Duncan M, Tallino S, Sandoval I, Manfredsson F, Velazquez R. Arizona State University; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Down Syndrome (DS) is a genetic disorder characterized by the triplication of chromosome 21, and is the leading contributor to the development of early onset Alzheimer's Disease (AD). By age 40, many individuals with DS show signs of AD pathology such as Amyloid-beta plaques and neurofibrillary tangles (NFTs). Dementia is also the leading cause of death for individuals with DS. In addition to memory loss and cognitive decline associated with neuronal loss, neuropsychiatric symptoms (NPSs) are common among AD patients typically presenting as anxiety or depression. Similarity, NPSs emerge in DS as one of the earliest clinical manifestations of dementia. Currently, the Ts65Dn mouse model is widely used to understand progression of memory and cognitive limitations and degeneration within DS. Importantly, this model shows age-dependent Basal Forebrain Cholinergic Neuron (BFCN) loss, which is present within human DS and AD. However, current mouse models for DS contain modest tau hyperphosphorylation, so the progression to NFTs does not occur. Therefore, to better model the progression of tau pathology within DS, our lab introduced humanized tau into the adult mice prior to the development of AD pathology. Due to the many BFCN projections to the amygdala, loss of these neurons may accelerate and increase NPSs such as anxiety-like behavior.

Methods: We used an adeno-associated virus (AAV) carrying two tauopathy mutations, the P301L mutation linked to frontotemporal dementia (FTD) and the S320F mutation linked to Pick's Disease. The AAV was delivered to the medial septum region of the basal forebrain (BF) to address the hypothesis that an introduction of humanized tau will increase overall due to the increased tau burden in brain regions associated with anxiety-like behavior. Additionally, the medial septum has been known to have indirect projections to the amygdala through the hippocampus. At 3 to 4 months of age, both sexes of the disomic Ts65Dn mice and trisomic Ts65Dn mice were sterotactically injected with either the AAV containing the humanized mutations (AAV-hTau2x), or a control virus (AAV-empty). At 9 months of age, behavioral testing was performed, including Elevated Plus Maze (EPM) to test anxiety-like phenotypes and the Rotarod to test motor function. At 10 months, the mice were euthanized, and their brains were collected to analyze the spread of both humanized and murine tau throughout the brain using immunohistochemistry.

Results: Behavioral results from the EPM reflect previous data showing lower anxiety indexes, greater amount of time in open arms, and more open arm entries for the trisomic Ts65Dn mice when compared to their disomic Ts65Dn littermates. However, AAV-hTau2x introduction to the BF did not elevate anxiety-like phenotypes.

Conclusions: Understanding how tau contributes to anxiety-like behavior and how it propagates throughout the brain may help guide the development of more effective treatments for NPSs. Future work utilizing immunohistochemistry will be used to determine tau spread and its presence in different brain regions associated with anxiety-like behavior.

STUDENT POSTER # 127

RENAL FUNCTION ADJUSTED PTAU217 IMPROVES DIAGNOSTIC PERFORMANCE AND COST EFFICIENCY FOR DETECTION OF AMYLOID PATHOLOGY. French SR, Wiskoski HE, Zahra S, Arias JC, Vitali F, Bedrick EJ, Mushtaq R, Dage JL, Ashton NJ, Pruzin JJ, Rapcsak SZ, Bornhorst JA, Algeciras-Schimnich A, Petersen RC, Reiman EM, Alexander GE, Weinkauf CC, The Health and Aging Brain Study (HABS-HD) Study Team, for The Alzheimer's Disease Neuroimaging Initiative. University of Arizona; Barrow Neurological Institute; Indiana University; Banner Alzheimer's Institute; Mayo Clinic Rochester; Arizona Alzheimer's Consortium.

Background: Although prior work has shown that renal dysfunction correlates with higher plasma pTau217 levels, it remains unclear whether adjustment for differences in renal function improves clinical interpretation of pTau217.

Methods: This multicenter cross-sectional cohort study assessed data from four independent US-based cohorts collected from 2005–2025: Health and Aging Brain Study: Health Disparities (HABS-HD, N=1736, 12.0% chronic kidney disease [CKD]), Wisconsin Registry for Alzheimer's Prevention (WRAP, N=301, 5.6% CKD), Alzheimer's Disease Neuroimaging Initiative (ADNI, N=277, 21.3% CKD), and Carotids and Minds (CAM, N=169, 24.9% CKD). Participants with plasma pTau217 and estimated glomerular filtration rate (eGFR) were included. HABS-HD, WRAP, and ADNI participants had Aβ positron emission tomography (PET) available. The effect of eGFR on plasma pTau217, diagnostic accuracy of plasma pTau217 and eGFR-adjusted pTau217 for Aβ PET, and cost-efficiency of eGFR-adjusted pTau217 based on total projected cost of false negatives ($8000), false positives ($30000), and confirmatory PET imaging ($4000) was assessed.

Results: 2483 participants were assessed (mean age 67.9, 61% female, 22% Black, 24% Hispanic, 13% CKD). Lower eGFR was associated with increased plasma pTau217 levels (β= -0.99, 95% CI [-1.14 – -0.83], P<0.0001). No association was observed between eGFR and Aβ PET (P=0.90). pTau217 adjustment for eGFR using residuals from log-log regression analyses improved diagnostic performance (ΔAUC=0.7%) and decreased the need for confirmatory Aβ PET scans by 4.3%, leading to increased cost-efficiency relative to unadjusted pTau217 (-$198,789.97 per 1000 cases). The greatest improvement associated with eGFR-adjusted pTau217 was observed in patients with CKD (ΔAUC=2.45%; relative reduction in confirmatory PET scans= 9.5%; relative cost reduction per 1000 CKD patients = $1,171,779.20).

Conclusions: pTau217 adjustment for eGFR improved classification of Aβ positivity and cost-efficiency, with most improvement seen in patients with CKD. eGFR-adjusted pTau217 may be useful in real-world aging and vascular patient populations that have a CKD prevalence of 20-30% or greater.

STUDENT POSTER # 128

THE RELATIONSHIP BETWEEN HIPPOCAMPAL ACVR1C EXPRESSION, SYNAPTIC DYSFUNCTION, AND SPATIAL MEMORY DECLINE IN HEALTHY AGING. Fritz MA, Bhuyian P, Huckabee SL, Keiser AA. Arizona State University; Arizona Alzheimer's Consortium.

Background: Hippocampal synaptic dysfunction drives age-related cognitive decline, yet the molecular mechanisms that maintain synaptic plasticity and preserve cognitive function remain poorly understood. ACVR1C serves as a bidirectional regulator of hippocampal-dependent memory in young mice and, when overexpressed in the dorsal hippocampus, can rescue age and AD-associated cognitive impairment in a hippocampus-dependent Object Location Memory Task (OLM) this study aims to further investigate the role of ACVR1C, a transforming growth factor-beta (TGF-β) type I receptor, in the aging brain, and whether these effects are mediated through presynaptic or postsynaptic mechanisms of synaptic plasticity.

Methods: Young 3-month (n=5 male, n=5 female) and 20-month-old (n=12 male, n=10 female) mice will undergo Object Location Memory (OLM) testing to evaluate spatial memory. Tissue will be taken 1 hour post-testing, followed by hippocampal quantification of ACVR1C, along with presynaptic (Synapsin I and Synaptophysin) and postsynaptic (PSD95) markers. Astrocyte and microglia involvement (GFAP and Iba-1) will also be assessed via Western Blot and immunofluorescence.

Results: We hypothesize that aging mice will exhibit parallel declines in hippocampal-dependent memory, ACVR1C expression, and synaptic protein levels compared to young mice. We further anticipate that individual expression of ACVR1C will positively correlate with both cognitive performance and markers of synaptic plasticity, suggesting a role of ACVR1C in pathway maintenance.

Conclusions: By establishing whether ACVR1C expression tracks with aging, this work aims to identify the functional correlation of cognitive decline and to provide a foundation for future studies investigating ACVR1C as a potential therapeutic target for cognitive aging and Alzheimer's Disease.

STUDENT POSTER # 129

LONGITUDINAL CORTICAL AGING AND CO-OCCURRING CHALLENGES IN MIDLIFE AND OLDER AUTISTIC ADULTS. Gallegos S, Zhang Y, Velez Galindo M, Johnson F, Bayouth C, Stein E, Harker S, Braden B. Arizona State University; Arizona Alzheimer's Consortium.

Background: Aging autistic adults are an expanding and understudied population. Daily functioning depends on integrated motor, language, and executive capacities; yet, lifelong challenges in these areas are all common co-occurring features of autism. Further, cortical brain networks scaffold these domains and are sensitive to age-related decline. More research that integrates longitudinal brain aging with cooccurring challenges is needed to fully understand aging in autistic people and identify the most effective lifespan supports. Objectives: 1. Evaluate longitudinal whole-brain cortical morphometry for potential areas of accelerated aging in autistic adults. 2. Identify co-occurring behavioral challenges that correlate with areas of brain aging vulnerability in aging autistic adults.

Methods: Participants were 112 autistic adults (diagnosis confirmed via ADOS-2) and 90 nonautistic controls (age equals 40.7 plus or minus 16.4; 18 to 71 years), and adults greater than or equal to 40 years of age (autistic adults: n equals 61; control: n equals 52) were invited for biennial follow (n equals 113). Whole-brain regional surface area (primary), thickness, and volume on white (i.e., gray/white matter interface) and pial surfaces were generated via FreeSurfer. Baseline metrics were evaluated for group by age interactions, and values from significant clusters (vertex-wise p less than 0.005, cluster-based p less than 0.05 using random field theory [RFT]) were extracted from all longitudinal scans for evaluation in multi-level models. Brain metrics were evaluated for exploratory relationships with executive functioning (Trails A/B; Stroop color-word interference), language (verbal fluency), and fine motor (finger tapping) measures using Spearman correlations (p less than 0.05, uncorrected).

Results: Autistic adults demonstrated evidence of greater age-related surface area loss in the left orbitofrontal and pars orbitalis/triangularis (Figure 1A and B; cluster equals 5134 vertices, RFT-corrected p less than 0.005, peak t equals 3.50) that was confirmed with longitudinal modeling (t equals 2.07, p equals 0.041) and precentral gyrus (Figure 1A; cluster equals 3367 vertices, RFT-corrected p equals 0.025, peak t equals 4.21) on the white surface, as well as in the left precentral gyrus (cluster equals 2616 vertices, RFT-corrected p equals 0.019, peak t equals 3.92) on the pial surface, compared to controls. Smaller orbitofrontal and pars orbitalis/triangularis white surface area correlated with poorer executive functioning (Trails A: r equals minus 0.33, p equals 0.0096, Figure 2A; Trails B: r equals minus 0.26, p equals 0.043; Stroop 3: r equals 0.34, p equals 0.0071, Figure 2B) and fine motor performance (finger tapping: non-dominant r equals 0.27, p equals 0.04; dominant r equals 0.33, p equals 0.011; total r equals 0.30, p equals 0.021, Figure 2C) in autistic adults. Smaller precentral pial surface area correlated with poorer fine motor performance (non-dominant: r equals 0.28, p equals 0.03) and semantic fluency (animal naming: r equals 0.28, p equals 0.032) which was also related to the precentral white surface area (animal naming: r equals 0.26, p equals 0.04, Figure 2D). In neurotypical controls, no behavioral variables correlated significantly with surface area in either cluster (all p greater than or equal to 0.05).

Conclusions: In one of the first longitudinal cortical brain aging investigations of older autistic adults, we identified frontal lobe gray and white matter regions that are potential vulnerable to accelerated decline. Further both areas correlated with various cooccurring challenges in motor, language, and executive functioning. However, these exploratory correlations should be interpreted with caution since results were not corrected for multiple comparisons. All findings should be replicated in other cohorts, but these preliminary results shed light on brain areas that may be particularly vulnerable to aging in autistic adults and the ramifications brain aging may have on co-occurring challenges.

STUDENT POSTER # 130

SHAPING MENOPAUSAL MEMORY BY PREGNANCY HISTORY: PARITY-INDUCED COGNITIVE IMPROVEMENTS ARE IMPACTED BY ABSENCE OF FEMALE GYNECOLOGICAL ORGANS. Garayzar Lopez A, Oevermann MW, Doyle RT, Diaz Z, Kaur I, Holappa KI, Gonzalez-Cruz I, Hannahs MK, Lizik CR, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.

Background: Pregnancy induces profound physiologic and behavioral changes in females with the evolutionary goal to optimize bidirectional survival of the mother and her young. Prior pregnancies, known as parity, induces enduring plasticity changes in the hippocampus, a brain region vital for learning and memory. Women have unique female-specific lifespan events including pregnancy and menopause. Notably, approximately 50% of women undergo some form of gynecologic surgery in their lifetime. Predominant gynecologic surgical procedures include uterus removal, hysterectomy, and ovarian removal, oophorectomy in women and ovariectomy (Ovx) in rats. There is evidence that each of these surgery types increase dementia risk in women, and our laboratory has been the first to show that each surgery type detrimentally impacts memory in rats. Few studies have investigated whether parity-induced cognitive changes are impacted by variations in menopause or reproductive tract removal. Indeed, the uniform focus of these studies thus far has been on the impact of ovarian removal. Given the clinical prevalence of hysterectomy as well as our data showing hysterectomy-induced memory detriments, whether parity outcomes are impacted by different gynecological surgeries including hysterectomy has important implications to women's health. Here, we address this critical knowledge gap by performing an experiment whereby we removed specific reproductive tract organs in rats with no prior pregnancy history (Non-parous condition), or with multiple prior pregnancies (Parous condition) to discern whether impacts from pregnancy extend to, and interact with, surgical menopause variants for cognitive function.

Methods: Non-parous and Parous rats were given Sham, Hysterectomy, or Ovx surgery, and then trained on the water-radial-arm-maze to determine spatial working and reference memory abilities as working memory load increased. Next, rats received the visual platform control task to assess motoric and visual competencies for water-maze procedural components. Body weights and vaginal smears were also tracked.

Results: Preliminary analyses indicate that parity enhanced performance only in rats that did not have reproductive tract organ removal, with the Parous Sham group making fewer errors than the Non-parous Sham group. Removal of the uterus or ovaries obviated these benefits. All rats successfully completed the control visible platform task thereby confirming competence to perform water-maze procedural components. Weight gain occurred in all rats across the experiment, and Ovx rats weighed more than other groups across the Parity condition. All estrous cycles persisted normally in groups with retained ovaries, and all Ovx groups exhibited the expected non-cyclic blank smears.

Conclusions: These preliminary results indicate that parity can enhance cognition, and that presence of specific reproductive tract organs can impact these outcomes. Additional research is ongoing to fully elucidate the influence of parity on the brain and behavior after variations in menopause-associated etiologies. The female lifespan is highly individualized and variable. Our findings build on prior studies showing that parity impacts later cognitive and brain health. This work underscores the importance of deciphering factors driving these outcomes, with a particular focus on critical endocrine shifts across the lifespan such as pregnancy and menopause.

STUDENT POSTER # 131

DISCOVERY OF DYR684, A HIGHLY POTENT AND METABOLICALLY STABLE DYRK1A/B DEGRADER. Ginn S, Schofield K, Wilms G, Foley C, Kallabis F, Becker W, Hulme C. University of Arizona; University of Bonn; RWTH Aachen University; Arizona Alzheimer's Consortium.

Background: Dual specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A) is a highly conserved protein kinase that plays a key role in cell differentiation and cell cycle regulation. Both amyloid precursor protein (APP) and tau protein are direct substrates of DYRK1a, with hyperphosphorylation of both APP and tau leading to Aβ plaques and neurofibrillary tangles (NFTs), two key hallmarks of Alzheimer's Disease (AD). Inhibition of DYRK1a using small molecules has been shown to reduce Aβ peptide and p-tau levels in vivo, elevating interest in DYRK1a as a therapeutic target. Outside of AD, DYRK1a inhibition has shown promise as a therapy for down syndrome and type I diabetes.

Methods: In this work, we aim to develop a Proteolysis-Targeting Chimera (PROTAC) capable of degrading DYRK1a. PROTACs are an innovative class of compounds that degrade target proteins in vivo via the proteasome, with vepdegestrant becoming the first FDA approved PROTAC in May 2026. Utilizing our previous research on small-molecule DYRK1a inhibitors, we synthesized a series of PROTACs conjugating our lead small molecule DYR530 to Von Hippel-Lindau (VHL) protein and Cereblon ligands with various linker lengths and sizes. We evaluated DYRK1a/b affinity by competition binding assay (Kd ELECT), and degradation in HEK293 cells by overexpressing HiBiT-tagged DYRK1 constructs. Additionally, degradation selectivity of a lead compound was assessed using quantitative global proteomic profiling in HEK293 and SH-SY5Y neuroblastoma cells.

Results: DYR684, which employs an extended rigid linker conjugated to the cereblon ligand pomalidomide, was identified as a potent dose dependent degrader of DYRK1a/b. DYR684 achieved a DYRK1a Kd of 6.3 nM, a DC50 value (the concentration at which half-maximal degradation is achieved) of 12.3 nM, and a Dmax of 90%. The PROTAC is metabolically stable with a 7.38 hour half-life in mouse liver microsomes. DYR684 was found to be largely selective for DYRK1a, with DYRK1a the only protein kinase to be significantly degraded upon treatment. Both WIZ and ZFP91, zinc finger proteins that have been identified as pomalidomide/lenalidomide-based neo substrates of cereblon, were also depleted upon treatment. In vivo pharmacokinetic studies via intraperitoneal injection revealed DYR684 is quickly taken up and has a relatively low clearance (T1/2 = 4.75 hours). However, the compound is not brain penetrant and is not orally bioavailable.

Conclusions: Overall, we have identified a selective, potent, and metabolically stable compound capable of sustained degradation of DYRK1a in vitro. With significant potential as a therapeutic intervention in Down Syndrome, Type I Diabetes, and Alzheimer's Disease, future work focuses on improvement of CNS permeability via enhancement of physicochemical properties and utilizing novel drug delivery techniques.

STUDENT POSTER # 132

DOES A PRIOR HISTORY OR ONGOING CHRONIC STRESSORS EXACERBATE AMYGDALA AND MEDIAL PREFRONTAL CORTEX CREB EXPRESSION IN MIDDLE-AGED VERSUS YOUNG ADULT RATS? Gonzalez AJ, Dorman JL, Olson N, Verpeut J, Conrad C. Arizona State University; Arizona Alzheimer's Consortium.

Background: Major depressive disorder (MDD) is a common psychiatric condition defined by persistent emotional dysregulation, cognitive impairments, and reduced quality of life. Women are diagnosed with MDD at about twice the rate of men with highest risks during middle age. Chronic stress is often used to model MDD in rodents with historic studies mainly using male subjects. Recently, cognitive fog was added in MDD symptomatology. Consequently, very few studies have investigated depression models using female rodents and included cognitive domains. Finally, concurrent and prior chronic stress exposures have different effects. Therefore, this study compared chronic stress (current and past) effects on spatial reference memory (requiring hippocampal function) and spatial working memory (requiring medial prefrontal cortex, mPFC) on brain plasticity measures using cAMP-response element binding protein, CREB.

Methods: Seventy-nine virgin, gonadally intact female Fischer-344 CDF rats were housed under a reverse light cycle (at 6 AM). Young (5 months) and middle-aged (12 months) rats were assigned to three experimental conditions: non-stressed controls (CON), stress-past (StrP; chronic stress completed two weeks before behavioral testing), and stress-concurrent (StrC; chronic stress started and maintained during behavioral testing). Chronic stress was induced using unpredictable intermittent restraint (UIR), involving restraint with mild agitation (30 to 60 minutes). Rats were tested in the Morris Water Maze (MWM) for spatial reference memory and the Radial Arm Water Maze (RAWM) for spatial working memory. After behavioral testing, rats were euthanized, and brain tissues processed for Western blot to quantify CREB protein expression. CREB expression was normalized to vinculin (1:10,000 dilution, using the same secondary antibody) as a loading control.

Results: Chronic stress (concurrent and past) improved spatial reference memory in both young and middle-aged females, albeit with different temporal parameters. In contrast, chronic stress had different and opposite effects in young and middle-aged female rats for working memory, with impairments in young and improvements in middle-age. Tissue processing for middle-aged females is ongoing and will be reported in greater detail in the poster, but we are analyzing changes in CREB expression in the mPFC amygdala and dorsal hippocampus.

Conclusions: Chronic stress alters cognition and neural plasticity-related signaling in brain regions linked to MDD and cognition in young and middle-aged female rats. Depending upon the cognitive domain investigated, chronic stress (StrC and StrP) had opposite effects in young adult female rats. In contrast, chronic stress improved spatial reference and working memory in middle-aged female rats. Stress-induced reductions in mPFC CREB expression align with the pattern observed in young adult female rats, but not with middle-aged female rats. As ovarian hormones can influence these cognitive domains and these rats were gonadally-intact, a possibility exists that some chronic stress effects may have been obscured. Future studies will investigate female rats with their ovaries removed. In addition, tissue processing is ongoing for the amygdala and dorsal hippocampus. We hope to determine whether CREB expression in one of these regions would correlate with behavior and stress exposure. Such an outcome would help to identify potential new neural pathways that may be in involved with female MDD risk.

STUDENT POSTER # 133

LIVER DYSFUNCTION INFLATES CIRCULATING PTAU217, HIGHLIGHTING BRAIN DERIVED PTAU217 AS A MORE RELIABLE BIOMARKER. Greig EE, Robb WH, Denkinger MN, Bouchal SM, Singh A, Hohman TJ, Dickson R, Jaramillo A, Ashton NJ, Koran MEI. Mayo Clinic Florida; Mayo Clinic Arizona; Banner Sun Health Research Institute; Vanderbilt University Medical Center; The Sahlgrenska Academy at The University of Gothenburg; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Blood-based measures of tau isoforms are increasingly used clinically to monitor and predict Alzheimer's disease (AD) pathology. Emerging evidence indicates that concentrations of peripheral biomarkers, including tau, are influenced by systemic organ dysfunction, confounding diagnosis and limiting widespread clinical utility. Current FDA-approved assays measure total tau (peripheral and central) and do not distinguish between protein abnormalities secondary to organ dysfunction and levels reflecting true brain pathology. In this study, we evaluate total and brain-derived (BD) MAPT, pTau181, pTau217, and pTau231 in patients ~4 weeks before and 4-12 months after liver transplant (LT) to assess the stability of these blood-based biomarkers across the extremes of liver function.

Methods: 55 patients over the age of 65 received a solid LT at Mayo Clinic Arizona. Serum concentrations of total and brain-derived (BD) MAPT, pTau181, pTau217, and pTau231 were assessed via the NULISAseq 120-plex CNS Panel. Linear mixed-effects models assessed changes in tau levels pre- to post-LT and associations with changes in liver function assessed via Model for End-Stage Liver Disease 3.0 (MELD) Score.

Results: Following LT, all total tau measures decreased after LT, as did BD-pTau181 and pTau231 at 4-months (β=-0.374, p=0.008; β=-0.887, p0.05). Similarly, improvement in liver function was associated with significant decreases in all total tau levels, BD-pTau181, and BD-pTau231, but not with changes in BD-MAPT and BD-pTau217.

Conclusions: All total tau biomarkers change following LT, including the clinically implemented pTau217, suggesting these biomarkers be interpreted with caution in patients with liver dysfunction. Of note, BD-MAPT and BD-pTau217 did not change post-LT, suggesting that these biomarkers may be more reliable in populations with organ dysfunction. Tau production and release from hepatocytes due to stress, or altered hepatic clearance of systemic tau, may be contributing to elevated levels of total tau compared to BD-tau. Total tau biomarkers including pTau217 should not be used in AD evaluation in pre-LT cases.

STUDENT POSTER # 134

CIRCULATING PROTEINS OF NEURODEGENERATION AND IMMUNE RESPONSE ARE ALTERED WITH LIVER TRANSPLANTATION. Greig EE, Robb WH, Denkinger MN, Bouchal SM, Singh A, Hohman TJ, Dickson R, Jaramillo A, Ashton NJ, And Koran MEI. Mayo Clinic Florida; Mayo Clinic Arizona; Banner Sun Health Research Institute; Vanderbilt University Medical Center; The Sahlgrenska Academy at The University of Gothenburg; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Global blood proteomics is increasingly being used in neurodegenerative diseases including Alzheimer's disease (AD), but understanding the influence of systemic organ function remains critical. The FDA approved the Lumipulse G pTau217/Aβ42 plasma ratio test to aid in diagnosis of AD. However, evidence indicates that these peripheral biomarkers are influenced by systemic conditions, including renal and liver dysfunction. In this study, we evaluated 131 plasma proteins in adults over 65 years of age at the Mayo Clinic Arizona, both before and after solid liver transplantation, to assess how changes in liver function impact circulating protein levels.

Methods: In total, 55 patients received a liver transplant between 2023-2024. Serum concentrations of proteins associated with neurodegeneration and immune function were assessed via the NULISAseq 120-plex Central Nervous System (CNS) Disease Panel approximately 4 weeks pre-transplant and 4-12 months post-transplant. Liver function at the different time points was quantified with the Model for End-Stage Liver Disease 3.0 (MELD) score. Linear mixed-effects models assessed changes in protein concentrations relative to changes in the MELD score.

Results: At either post-LT time point, 109/131 (84%) of CNS disease panel proteins significantly changed. 72 proteins were significantly different at both 4- and 12-months post-LT and changed in consistent directions. Of these 72 consistent proteins, 51 decreased after LT and 21 increased after LT. The greatest proportion of DNA and/or RNA defects, Altered Energy Homeostasis, and Pathological Protein Aggregation -classified proteins changed post-LT (using Alamar classification; 75%, 3 proteins; 70%, 7 proteins; 63%, 12 proteins, respectively). At 4-months post-LT, strongest associations were observed in protein concentrations of NPTX1, BACE1 and ACHE (β=-0.899, β=-0.778, β=-0.983; all $p<0.001$), and at 12-months post-LT, strongest associations were with VCAM1, FCN2, and DDC (β=-0.974, β=2.248, β=-1.595; all $p<0.001$). Associations were similar when assessing quantitative liver function using MELD.

Conclusions: This study suggests that circulating plasma proteins associated with CNS processes and immune response are altered due to liver dysfunction, perhaps due to alterations to hepatic clearance, production, or inflammatory pathways. Of note, top protein changes were in NPTX1, BACE1, and ACHE, proteins linked to synaptic function, amyloid precursor protein proteolytic processing, and acetylcholine synaptic signaling termination. Future studies are needed to validate these findings in a larger cohort and compare elevations in protein concentrations to true neurodegenerative pathology cases.

STUDENT POSTER # 135

PERCEIVED STRESS AND COGNITIVE FUNCTION IN A DIVERSE COHORT: DOMAIN-SPECIFIC ASSOCIATIONS FUNDING. Guareña LA, Venkatachalam H, Johnson M, De Both M, Huentelman M, Ryan L, The Precision Aging Network. University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Higher perceived stress is linked to poorer cognition and increased risk of decline, yet less is known about this association in diverse populations or across cognitive domains. This study examined associations between perceived stress and episodic memory and attentional processing, and differences among Hispanic/Latino, Non-Hispanic Black (NHB) and Non-Hispanic White (NHW) adults.

Methods: Data were analyzed from the MindCrowd online observational study. Episodic memory and reaction time analyses included 4,127 and 4,070 participants, respectively. Participants completed the Perceived Stress Scale, verbal paired associates learning, and simple visual reaction time tasks. Multivariable linear regression models examined associations between perceived stress and cognitive performance, adjusting for age, sex, educational attainment, and race/ethnicity. Reaction time models additionally adjusted for device type. Perceived stress by race/ethnicity interactions were examined.

Results: Hispanic/Latino participants reported the highest perceived stress levels ($p < .001$). NHW participants demonstrated better episodic memory and faster reaction times than Hispanic/Latino participants, whereas NHB participants demonstrated poorer episodic memory and slower reaction times (all ps $< .001$). Higher perceived stress was associated with poorer episodic memory ($\Delta R^2 = .002$, $\Delta F(1, 4119) = 7.89$, $p = .005$), and the perceived stress by race/ethnicity interaction was not significant ($\Delta F(2, 4117) = 2.26$, $p = .104$). In contrast, the perceived stress by race/ethnicity interaction was significant for reaction time ($\Delta R^2 = .002$, $\Delta F(2, 4058) = 4.62$, $p = .010$). Higher perceived stress was associated with slower reaction times among NHW participants ($B = 1.08$, $SE = 0.32$, 95% CI [0.45, 1.70], $p < .001$), but not Hispanic/Latino or NHB participants.

Conclusions: Associations between perceived stress and cognition varied by cognitive domain. Perceived stress was associated with poorer episodic memory, with no evidence that this association differed by race/ethnicity, whereas its association with reaction time differed by race/ethnicity. These findings underscore the importance of considering cognitive domain and racial/ethnic context when examining associations between psychosocial stress and cognition.

STUDENT POSTER # 136

NOVEL CONFORMATION-SPECIFIC ANTIBODIES ENABLE DETECTION OF FRONTOTEMPORAL DEMENTIA-ASSOCIATED BIOMARKERS IN HUMAN SERUM. Hanna B, Sierks M. Arizona State University; Arizona Alzheimer's Consortium.

Background: Frontotemporal dementia (FTD) is a progressive neurodegenerative disorder characterized by early degeneration of frontal and temporal brain regions, resulting in profound behavioral, cognitive, and language impairments. Because significant neuronal damage is often present before clinical symptoms become apparent, biomarkers capable of identifying early or pre-symptomatic disease states would provide substantial diagnostic and therapeutic value. Current diagnostic approaches rely heavily on clinical presentation and neuroimaging, which may lack sensitivity during the earliest stages of disease progression.
Accumulating evidence suggests that soluble oligomeric and misfolded protein species represent the most toxic and disease-relevant forms of neurodegenerative pathology. In particular, aberrant TDP-43 species have emerged as a major pathological hallmark in a large subset of FTD cases and may serve as promising blood-based biomarkers for early disease detection. We developed a panel of conformation-selective binding reagents designed to recognize disease-associated oligomeric protein variants and evaluated their ability to distinguish FTD-associated serum samples from cognitively normal controls using a multiparameter blood-based assay.

Methods: A panel of conformation-selective IgG antibodies developed in our laboratory and synthesized by GeneScript was utilized in a sensitive sandwich ELISA platform to detect disease-associated biomarker variants present in human serum samples. IgG-based antibodies were used as capture antibodies while IgG versions of pan-specific anti-TDP-43 and anti-tau detection reagents were employed as detection antibodies. Bound detection antibodies were identified using avidin-HRP secondary detection and quantified by electrochemiluminescence (ECL).
Statistical analyses were performed using RStudio and ggplot2 library (R Core Team, 2024) plug-in. Independent samples t-tests and one-tailed bivariate correlations were conducted at $p < 0.05$ to evaluate biomarker significance. Receiver operating characteristic (ROC) curve analysis was additionally performed to assess assay sensitivity and specificity.

Results: Preliminary analysis identified multiple biomarker-reactive profiles that significantly differentiated FTD-associated serum samples from cognitively normal controls. Several conformation-selective reagents targeting oligomeric TDP-43 variants demonstrated elevated binding patterns in FTD samples relative to controls, suggesting the presence of disease-associated circulating protein species detectable in blood serum.
Multiparameter analysis further suggested that combinations of biomarker signals may provide greater discriminatory power than individual markers alone. ROC analysis demonstrated excellent sensitivity and specificity for distinguishing FTD-associated samples from controls, supporting the potential utility of a blood-based biomarker panel for early-stage disease detection.

Conclusions: These findings support the feasibility of a simple multiparameter blood-based assay utilizing conformation-selective reagents targeting oligomeric TDP-43 variants for the early detection of FTD-associated pathology. The ability to identify disease-relevant biomarker signatures in serum may provide a minimally invasive strategy for improving early diagnosis, monitoring disease progression, and potentially identifying individuals during preclinical stages of neurodegeneration.
Further studies with expanded cohorts will be necessary to validate biomarker specificity, determine longitudinal predictive value, and evaluate the broader applicability of this approach across diverse FTD subtypes.

STUDENT POSTER # 137

AUTISM GENETIC LIABILITY IN ALZHEIMER'S DISEASE AND RELATED NEUROPATHOLOGY. Harker SA, Serrano G, Aslam S, Piras IS, Shablin AS, Huentelman MJ, Taguinod F, Braden BB, Lewis CR. Arizona State University; Banner Sun Health Research Institute; Translational Genomics Research Institute; University of Utah; Arizona Alzheimer's Consortium.

Background: Multiple independent healthcare record sources have demonstrated that adults with autism spectrum disorder (ASD) are at increased risk for Alzheimer's disease (AD) and related dementias. The biological mechanisms driving the convergence between neurodevelopmental and neurodegenerative conditions are largely unknown. Autism has a strong genetic basis with heritability estimates ranging from 50-80%; therefore, autism genetic liability may confer risk for AD and related neuropathology.

Methods: Neuropathology-confirmed AD diagnoses included 466 cases and controls included 258 without mild cognitive impairment/dementia during life and a major neuropathological diagnosis. No participants had known ASD diagnoses. Autism polygenic risk scores (PGS) were generated, and participants were binned into ASD-PGS quartiles with Q1 as the bottom 25% of least risk and Q4 as the top 25% greatest risk. The Consortium to Establish a Registry for Alzheimer's Disease templates were used to score tangles and plaques as none, sparse, moderate, and frequent, converted to 0-3 for analysis.

Results: PGS quartiles were used to model non-linear relationships and aid in interpretation. All models adjusted for postmortem interval, age at death, gender, the AD-PGS, and the first 9 principal ancestry components. Autism-PGS was associated with AD status with individuals in the highest risk quartile (Q4) exhibiting the highest odds of AD compared to Q1-3 ($p<0.05$). In controls, Autism-PGS was associated with greater plaque burden across multiple regions and entorhinal tangle burden (all p's<0.05 false discovery rate [FDR] corrected), but there were no Autism-PGS associations in AD cases, consistent with a ceiling effect of pathology.

Conclusions: Findings indicate that autism genetic liability may reflect shared biological pathways influencing AD neuropathology. Importantly, with the relatively recent (1980) inclusion of autism in the DSM, adults with confirmed autism diagnoses have historically not been included in AD neuropathology research. Therefore, many of the participants in the highest quartile of ASD genetic liability could be undiagnosed autistic adults. These are some of the first biological insights on the convergence of ASD and AD diagnosis, which suggest potentially greater canonical AD neuropathology associated with autism, as opposed to autism-specific brain aging mechanisms alone. Future neuropathology research in those with confirmed autism diagnoses is warranted. Elevated autism polygenic risk may contribute to variability in AD risk and neuropathology.

STUDENT POSTER # 138

EARLY RISK, LASTING IMPACT: ADVERSE CHILDHOOD EXPERIENCES AND EXECUTIVE FUNCTIONS IN HISPANIC/LATINO VS. NON-HISPANIC WHITE OLDER ADULTS. Hendrickson N, Guareña L, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.

Background: Adverse childhood experiences (ACEs) have been associated with adverse physical, mental, and cognitive outcomes, yet relatively few studies have examined their relationship with executive functions in older adulthood or whether these associations differ by race/ethnicity.

Methods: This study examined associations between ACE exposure and executive functions among 80 adults aged 50–79 years (40 Hispanic/Latino, 40 Non-Hispanic White) recruited from the Healthy Minds for Life study. ACE exposure was assessed using a modified Childhood Trauma Questionnaire, and performance was evaluated using computerized measures of working memory updating (Keep Track), inhibitory control (Flanker), and cognitive flexibility (Letter Number). Separate multiple linear regression models examined ACE exposure continuously (total score out of 21) and categorically (0, 1–7, and ≥8 ACEs). ACE × race/ethnicity interaction models tested whether associations differed by race/ethnicity, adjusting for sex, education, and age.

Results: No significant associations were observed between continuous or categorical ACE exposure and accuracy-based measures, and ACE × race/ethnicity interaction terms were nonsignificant across all accuracy outcomes. Hispanic/Latino participants demonstrated lower Keep Track Accuracy than Non-Hispanic White participants after adjustment for demographic covariates, although this difference did not reach statistical significance (B = -12.00, SE = 6.99, p = .091). Participants reporting ≥8 ACEs demonstrated longer Letter Number reaction-time differences (p = .066) and reduced switch-task efficiency (p = .089) relative to participants reporting no ACEs, although neither association reached statistical significance.

Conclusions: Overall, ACE exposure was not significantly associated with executive functions. Trend-level findings on measures of cognitive flexibility warrant further investigation in larger samples.

STUDENT POSTER # 139

WHITE MATTER CHANGES IN ALZHEIMER'S DISEASE WITHIN A LATIN-AMERICAN POPULATION. Hickey R, Guss P, Huggins A, Flores M, Grilli M, Chou Y-H. University of Arizona; Arizona Alzheimer's Consortium.

Background: White matter alterations are well-documented in Alzheimer's disease (AD) and behavioral variant frontotemporal dementia (bvFTD). Diffusion tensor imaging (DTI) studies have shown promise in distinguishing between disease type and stage. Prior studies have demonstrated reduced fractional anisotropy (FA) and increased mean diffusivity (MD) within disease-relevant white matter pathways in individuals with AD and FTD relative to cognitively normal controls. However, much of this evidence relies on demographically homogeneous cohorts that are predominantly non-Hispanic White, highly educated, and based in North American or European settings, limiting our ability to generalize established DTI patterns to other populations. The present study examines whether DTI-derived white matter metrics differ among cognitively normal adults and individuals with AD, and bvFTD in a Latin American cohort.

Methods: This study used data from the Bogotá, Colombia site of the publicly available Latin American Brain Health Institute dataset. The total sample included 139 individuals: CN (n = 43), AD (n = 20), and bvFTD (n = 76). Data from this study included structural and diffusion-weighted MRI, cognitive screening, and self-reported demographics. Diffusion imaging data were processed using the standardized ENIGMA pipeline and tract-based spatial statistics. Group comparisons were conducted using voxel-wise nonparametric permutation testing with threshold-free cluster enhancement, controlling for age, sex, and education. Pairwise contrasts examined differences between AD-CN, bvFTD-CN, and AD-bvFTD groups. Primary analyses included predefined tracts of interest for AD (i.e., the corpus callosum, hippocampal cingulum, and fornix) and FTD (i.e., the corpus callosum, uncinate fasciculus, and cingulum bundle). Exploratory whole-skeleton analyses were also conducted. Statistical significance was determined using TFCE-corrected p-value images, with results thresholded at p less than .05.

Results: Relative to cognitively normal adults, individuals with AD demonstrated significant reductions in FA within the corpus callosum. Exploratory analysis also showed differences in multiple association fibers, including the superior longitudinal fasciculus and the cingulum. In the bvFTD and CN comparison, significant MD differences were observed within the corpus callosum and additional association fibers (e.g., uncinate fasciculus, anterior cingulum, and superior fronto-occipital fasciculus). Across contrasts, findings indicated that DTI detected some disease-related white matter abnormalities relative to cognitively normal adults but did not distinguish AD from bvFTD.

Conclusions: These findings provide partial support for the generalizability of DTI-based white matter markers in a Latin American neurodegenerative disease cohort. White matter differences were observed in expected disease-relevant pathways, particularly involving the corpus callosum, supporting the utility of DTI for detecting neurodegeneration-associated white matter abnormalities beyond predominantly North American and European samples. These findings highlight both the promise and limitations of traditional DTI as a ubiquitous measure of white matter integrity and underscore the importance of demographically inclusive neuroimaging research.

STUDENT POSTER # 140

EFFECTS OF EXERCISE ON COGNITIVE PERFORMANCE AMONG OLDER ADULTS. Ho G, Matijevic S, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.

Background: Among older adults, poor cardiovascular health is associated with worse performance in numerous cognitive domains. Since exercise improves cerebrovascular function, exercise might protect cognition against poor cardiovascular health. Some studies have found protective effects of exercise on cognition, but others have not. One potential explanation for this discrepancy is that certain individuals benefit more from exercise than others. We hypothesize that individuals with severe cardiovascular dysfunction might have less capacity to benefit from exercise than those with more moderate cardiovascular health issues.

Methods: This study investigates how cardiovascular health and level of physical activity interact to affect cognition among older adults. We plan to analyze data from approximately 700 adults aged 50-79, who participated in the Precision Aging Network's multisite study of cognitive aging. Activity levels are measured through Garmin watch actigraphy and lifestyle questionnaires, namely the Quick Physical Activity Rating (QPAR). Episodic memory recall is assessed through the Auditory Verbal Learning Test (AVLT), while working memory updating is assessed through the Keep Track test.

Results: In our analysis, levels of physical activity as measured by QPAR total were not associated with either AVLT long delay free recall or Keep Track working memory scores after adjusting for age and sex. Planned additional analyses include assessing associations between medium/high intensity physical activity (as measured by Garmin actigraphy) with AVLT long delay free recall and Keep Track working memory scores.

Conclusions: Results indicate that total physical activity levels are not associated with cognitive performance among older adults. While we expect that exercise generally benefits cognition, this effect may depend on other factors. Specifically, we predict that level of cardiovascular health is an important moderator of the relationship between exercise and cognition. Findings from this study may imply a need to consider individual differences in exercise interventions. This research was funded by the National Institute on Aging [U19AG065169].

STUDENT POSTER # 141

PSMAD2 DEPENDENT REGULATION OF MOLECULAR AND PLASMA BIOMARKERS IN THE AGING BRAIN. Huckabee SL, Bhuiyan P, Shahub S, Fritz MA, Ashton NJ, Keiser AA. Arizona State University; Banner Sun Health Research Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Exercise is a key regulator for epigenetic mechanisms that promote learning and memory. Acvr1c is a bidirectional regulator of learning and memory that is upregulated when exercise facilitates learning in the hippocampus, a key brain region for spatial memory. The hippocampus is one of the earliest and most prominently affected brain regions in Alzheimer's disease (AD), showing early structural and functional changes that contribute to memory impairment. Projections from the CA1 region in the dorsal hippocampus to the prefrontal cortex (PFC) that are essential for learning and long-term memory formation may be dysregulated in AD. ACVR1C forms a complex with a type II TGF-beta receptor to phosphorylate SMAD2. SMAD2 functions as an epigenetic regulator through recruitment of cofactors that facilitate transcription. In aging individuals and those with Alzheimer's Disease, pSMAD2 is mislocalized in the cytoplasm, preventing it from entering the nucleus to induce transcription. Blood biomarker tests are rapidly developing as a non-invasive method to detect early signs of neurodegenerative disease. Plasma biomarkers like pTau181, pTau217, and pTau231 are currently used to identify individuals with AD.

Methods: This project aims to further investigate the effects of pSMAD2 by using blood and prefrontal cortex (PFC) tissue to identify changes in the plasma signatures when phospho-mimic S464D, S465D, S467D is overexpressed. We infused 20-month old C57Bl/6 aged mice in the CA1 region of the dorsal hippocampus (DHPC) with an AAV1 vector carrying a Smad2 phospho-mimicS464D, S465D, S467D (n=10: 5 female, 5 male). Phospho-mimic Smad2 S464D, S465D, S467D contains altered serines in the C-terminal to create an "always-phosphorylated" form of SMAD2. An empty vector (EV) group (n=9: 4 female, 5 male) was included in the stereotaxic surgeries using an empty AAV1 vector as a control. We also included a baseline control group (n=9: 4 female, 5 male) that received no manipulations. We will use subcellular fractionation to assess pSMAD2 localization in prefrontal cortex tissue and conduct a NULISA assay on plasma and whole PFC lysates to capture protein profiles. We will validate CA1 expression of our vectors using immunohistochemistry and examine sex differences.

Results: We hypothesize that the EV and baseline control groups will have higher concentrations of neurodegenerative and AD-associated blood biomarkers, specifically phosphorylated tau and other inflammatory markers. As the dorsal hippocampus signals to the PFC during long-term memory formation and consolidation, we hope to see a restorative effect in the molecular markers associated with learning in the PFC. Our studies will reveal whetherthe Smad2 phospho-mimic S464D, S465D, S467D will restore levels of phospho-tau and other associated biomarkers.

Conclusions: Using blood as a potential method to test for neurodegenerative biomarkers improves accessibility, comfort, and preventative early detection options for patients. Ultimately, we hope to uncover plasma proteins that serve as peripheral biomarkers of SMAD2 pathway activation and correlate them with molecular markers measured in the PFC. This study will identify plasma biomarkers that are rescued by SMAD2 pathway activation and determine the effectiveness of plasma protein analysis as a reflection of pSMAD2 activity in the DHPC and PFC.

STUDENT POSTER # 142

MEMORY INSPIRED MODELING OF ALZHEIMER DISEASE PROGRESSION USING KNOWLEDGE GRAPH DRIVEN ARTIFICIAL INTELLIGENCE. Javed A, Pan R. Arizona State University; Arizona Alzheimer's Consortium.

Background: Alzheimer disease progression is difficult to model because cognitive decline, brain atrophy, medication history, and diagnostic conversion unfold across multiple clinical visits rather than a single time point. Standard machine learning models and large language models often treat records as isolated snapshots, missing the order and meaning of longitudinal change. Although the disease is defined by progressive memory loss, many artificial intelligence systems lack structured memory to track disease evolution. This can produce unstable forecasts, poor temporal reasoning, and unsafe recommendations when biological constraints are absent. This project addresses that gap through a knowledge graph framework representing patient timelines, clinical similarity, and biological rules as connected memory structures.

Methods: This research presents Model C3, a distributed multi-agent system that grounds large language model reasoning in a high-fidelity Neo4j knowledge graph built from 1,730 longitudinal patient timelines. The architecture includes a macro knowledge graph containing global clinical statistics and biological constraints and a micro knowledge graph connecting patients through clinical twin relationships. Similarity was calculated using weighted Euclidean distance across cognitive scores, diagnostic state, and neuroimaging-derived atrophy patterns. Model C3 uses three agents: a diagnostic agent that queries clinical twins to forecast 36-month disease state, a chronology agent that reconstructs blinded event order after timestamps are removed, and a safety agent that blocks contraindicated medications, including Memantine use in mild cognitive impairment. Model C3 was compared with Model C0, a stateless baseline, and Model C1, a semantic retrieval baseline, using forecasting accuracy, temporal sequencing, and medication safety.

Results: The knowledge graph was successfully validated against global Alzheimer disease benchmarks. The extracted 46.0 percent mild cognitive impairment to dementia conversion rate over 4.1 years closely matched the reported Alzheimer Disease Neuroimaging Initiative baseline of 47.3 percent. The graph also identified a 3.9 percent annual hippocampal atrophy rate, within the expected 3.6 percent to 4.6 percent range for mild cognitive impairment to Alzheimer disease progressors. A biomarker cognition correlation of 0.73 further confirmed a strong relationship between brain volume loss and cognitive decline. Model C3 achieved the strongest performance across the main evaluation tasks. For forecasting Month 36 diagnostic conversion from Month 12 data, Model C3 achieved 94.2 percent accuracy, compared with 61.2 percent for Model C1 and 26.4 percent for Model C0. In blinded temporal sequencing, Model C0 and Model C1 achieved 0.0 percent accuracy, while Model C3 achieved 15.5 percent. Model C3 also actively queried the graph to block contraindicated medication recommendations, achieving a 94.6 percent success rate. These results demonstrate substantial gains in clinical forecasting, temporal reasoning, and active safety enforcement.

Conclusions: Grounding large language models in a validated knowledge graph improved longitudinal Alzheimer disease modeling while enforcing biological and medication safety constraints. Model C3 combined clinical twin retrieval, blinded temporal sequencing, and deterministic safety enforcement within a unified multi-agent architecture. Compared with both baselines, Model C3 achieved substantially higher Month 36 forecasting accuracy and uniquely demonstrated active medication guardrail behavior. These findings support knowledge graph-driven artificial intelligence as an interpretable, safety-aware framework for Alzheimer disease decision support. Future work will expand external validation, incorporate additional multimodal biomarkers, and evaluate the architecture in clinically realistic workflows.

STUDENT POSTER # 143

DEVELOPMENT OF DYR533, A HIGHLY SELECTIVE AND ORALLY BIOAVAILABLE INHIBITOR OF DYRK1A TOWARD THE TREATMENT OF ALZHEIMER'S DISEASE AND/OR DOWN SYNDROME. Kaleeswaran V, Rokey S, Foley C, Bartholomew S, Winslow W, Velazquez R, Dunckley T, Hulme, C. University of Arizona; Arizona State University - Banner Neurodegenerative Disease Research Center; Iluminos Therapeutics LLC; Arizona Alzheimer's Consortium.

Background: By 2050, it is projected that Alzheimer's Disease (AD) will affect 106 million people worldwide. Currently, there are no effective therapies to ameliorate the pathological progression and the associated cognitive deficits in AD. Therefore, targeting AD pathology via a single pathway is likely impossible, and a successful therapeutic strategy may require pleiotropic interventions. Dual specificity tyrosine phosphorylation regulated kinase-1A (DYRK1A) is an emerging target for the treatment of neurodegenerative diseases, as it has functional activity on multiple pathways implicated in AD and neuronal function. Through selective inhibition of DYRK1A, it may be possible to reduce both amyloid precursor protein (APP) dysregulation and tau hyperphosphorylation. The DYRK1A gene is also located within the Down Syndrome (DS) critical region on chromosome 21, and its overexpression is a significant contributor to the underlying neurodevelopmental and AD-like pathology associated with DS.

Methods: A structure-guided medicinal chemistry approach was used to design and optimize selective small-molecule inhibitors of DYRK1A. Two known inhibitors of DYRK1A, harmine and D15, were combined to arrive at an initial hit, DYR219. Lead optimization was performed to improve potency, selectivity, metabolic stability, and oral bioavailability. The compounds were evaluated using kinase inhibition assays, KinomeScan profiling against 468 kinases, ADME and pharmacokinetic studies, and safety pharmacology assays. The therapeutic efficacy of some lead compounds was assessed in the 3xTg-AD mouse model following oral administration for two months, with subsequent analysis of degradation of DYRK1A, delay of amyloid plaque formation, amount of phosphorylated tau, neurofibrillary tangles, amyloid-beta42, and inflammatory markers like TNF-alpha.

Results: Lead optimization yielded DYR533, a highly potent and selective DYRK1A inhibitor with a binding affinity (Kd) of 1.4 nM and a IC50 of 6 nM. KinomeScan profiling of DYR533 showed that it is an exceptionally selective molecule with a S(35) score of 0.028 at 1 μM. The compound also possessed favorable physicochemical and pharmacokinetic properties, including high passive membrane permeability, excellent microsomal and hepatocyte stability across multiple species, and good aqueous solubility. The compound achieved oral bioavailability of 100% in mice. Safety evaluation showed a favorable profile, including minimal cytochrome P450 inhibition, absence of significant hERG liability, and negative micronucleus genotoxicity. In the 3xTg-AD mouse model, oral administration of DYR533 for two months produced dose-dependent reductions in soluble and insoluble phosphorylated tau (Ser396) in both the cortex and hippocampus, accompanied by a marked reduction in neurofibrillary tangle formation.

Conclusions: A ten-year effort has led to the discovery of DYR533: a highly selective, orally bioavailable, brain-penetrant, well-tolerated small molecule inhibitor of DYRK1A which upon dosing in the 3xTgAD model elicits reductions in phospho-tau and neurofibrillary tangles in a dose dependent fashion. Studies are ongoing evaluating effects on amyloid pathology and neuroinflammation. DYR533 has been manufactured (GMP-grade) in kilogram scale and is ready for IND-enabling studies. Collectively, these findings demonstrate that DYR533 combines excellent drug-like properties with robust in vivo efficacy, supporting its continued development as a disease-modifying therapeutic candidate for Alzheimer's disease and related neurodegenerative disorders.

STUDENT POSTER # 144

MICROSTRUCTURAL ALTERATIONS SURROUNDING WHITE MATTER HYPER-INTENSITIES IN THE PRECISION AGING NETWORK COHORT. Karakay D, Ugonna CP, Matijevic S, Chen NK, Trouard TP, Ryan L, Altbach MI, Bilgin A. University of Arizona; Arizona Alzheimer's Consortium.

Background: White matter hyperintensities (WMHs) on FLAIR are common in aging and vascular disease and are markers of small-vessel pathology and cognitive decline. Although WMHs appear hyperintense on FLAIR, microstructural damage can extend beyond visible lesions into normal-appearing white matter (NAWM). Diffusion MRI provides quantitative measures of microstructural integrity. We analyzed the spatial extent of WMH-related abnormalities in the Precision Aging Network (PAN) cohort.

Methods: Data were drawn from cognitively normal older adults enrolled in the PAN study. All participants underwent multishell dMRI, high-resolution T1-weighted (T1w), and FLAIR scans at 3T across four sites. Diffusion-weighted images (DWIs) were obtained at b=0/500/1000/2000 seconds per square millimeter with uniformly distributed directions over the sphere. A reverse PE acquisition was also collected for susceptibility distortion correction. Data were preprocessed with qsiprep and reconstructed to generate DTI and NODDI maps, then transformed into T1w space using ANTS. White matter masks (WM) were derived using FSL FAST, and T1-w and co-registered FLAIR images were segmented with LST-AI to obtain WMH masks. The WMH penumbra was defined by computing the Euclidean distance from each NAWM voxel to the nearest WMH voxel and binning distances in 1 mm steps up to 15 mm. For each diffusion metric, a multivariate mixed-effects linear regression model was fitted with age, sex, and log (WMH load) as fixed covariates and random intercepts for subject and site. Adjacent distance shells were contrasted using forward difference coding.

Results: The cohort was largely non-pathological, with median WMH load less than one percent. Diffusion metrics within WMHs varied across major white matter regions, highlighting heterogeneity within WMH microstructure. All DTI and NODDI measures differed between WMH and the adjacent one-millimeter shell, with p less than 0.001. Between 1 to 5 mm, significant progressive normalization was observed: AD, ADC, RD, and ISOVF decreased while FA and ICVF increased with distance, indicating recovery of white-matter integrity. Beyond 6 mm, inter-shell differences vanished for all metrics except OD, indicating diffusion properties returned to NAWM levels. Log (WMH load) showed the strongest global effect, linking higher lesion burden to increased diffusivity and reduced fractional anisotropy and intracellular volume fraction.

Conclusions: Diffusion microstructure within WMHs is heterogeneous across major WM regions. Mixed-effects analysis of DTI and NODDI metrics in PAN cohort reveals a microstructural gradient extending approximately 5 millimeters beyond WMH borders. These abnormalities support a WMH penumbra that may serve as an early biomarker of white matter vulnerability in brain aging.

STUDENT POSTER # 145

ANTIOXIDANT GENE EXPRESSION IN SH-SY5Y CELLS UNDER METABOLIC AND OXIDATIVE STRESS: A QPCR STUDY IN AN ALZHEIMER'S DISEASE MODEL. Karg C, Patrick K, Akamangwa L, Oliver J, Richards R III, Clifford A, Ahmetovic A, David Moses GS, Nural-Guvener H. Grand Canyon University.

Background: Metabolic dysfunction is a precursor to and exacerbates the neurodegenerative symptoms of Alzheimer's disease (AD). Diabetes mellitus (DM) and AD share pathological mechanisms, including insulin resistance, glycolytic suppression, amyloid beta aggregation, advanced glycation end-product (AGE) accumulation with elevated AGE-RAGE signaling, and mitochondrial dysfunction, that converge on chronic oxidative stress (OS). However, how metabolic dysfunction alters neuronal antioxidant responses and contributes to AD progression remains unclear. Physiologic insulin signaling supports metabolic activity, neuronal survival, and nuclear factor erythroid 2-related factor 2 (Nrf2)-dependent activation of genes controlled by the antioxidant response element (ARE). Glyceraldehyde (GA), a glycolytic inhibitor targeting GAPDH, induces AD-like neurotoxicity and AGE formation, modeling metabolic dysfunction-driven oxidative stress. Elevated AGE levels during metabolic stress upregulate AGE-RAGE signaling and NF-kappa B, amplifying oxidative stress and driving neurons into a pro-inflammatory, pro-apoptotic state. This study examines antioxidant and AD-related gene expression in SH-SY5Y neuroblastoma cells subjected to metabolic versus canonical oxidative stress.

Methods: SH-SY5Y cells were treated with 65 uM hydrogen peroxide (H2O2) to induce oxidative stress or 1.5 mM GA to induce metabolic stress and compared to each other and with untreated controls in 6-well treatment plates. Total RNA was extracted, quantified, and assessed for purity, followed by reverse transcription and qPCR to evaluate relative expression of BACE1, CATALASE, GAPDH, GPX4, and SOD1 using the delta delta Ct method.

Results: qPCR conditions were optimized to ensure primer specificity (single melt peaks) and acceptable efficiency for all targets and treatments. HPRT-1 expression showed inconsistency and high-threshold cycles under treatment conditions.

Conclusions: To find reliable housekeeping genes under oxidative and metabolic stress, the genes HPRT1 & 18S have been tested. HPRT1 has not yet yielded consistent results. Meanwhile, successful validation and optimization of target primers under treatment conditions enable reliable quantification of differential gene expression. To further explore crosstalk between the AGE-RAGE and Insulin/PI3K/Akt/Nrf2 pathways, we will quantify AGER expression alongside GPx1, GPx3, NF-κB, and SIRT1.

STUDENT POSTER # 146

PHENOME-WIDE ASSOCIATION STUDY FRAMEWORK FOR IDENTIFYING CLINICAL CORRELATES OF ALZHEIMER'S DISEASE AND GENETIC RISK IN EHR-LINKED COHORTS. Kaur G, Robb WH, Koran ME. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is a complex neurodegenerative disorder influenced by genetic, environmental, and clinical factors. Although numerous genetic risk loci have been identified, less is known about the broad spectrum of clinical phenotypes associated with AD susceptibility across real-world healthcare settings. Phenome-wide association studies (PheWAS) provide a systematic framework for evaluating relationships between genetic risk factors and thousands of clinical diagnoses captured within electronic health records (EHRs). We developed an EHR-linked PheWAS framework to support large-scale investigation of clinical correlates of AD and AD-related genetic risk.

Methods: Participants were assembled from the Mayo Clinic Biobank and Mayo Clinic Tapestry Study, incorporating genetic and longitudinal EHR data. The framework integrates genotype information from 116,343 Biobank participants, 98,120 Tapestry exome participants, and 98,075 Tapestry imputed participants with EHR-derived clinical data containing over 19.4 million diagnosis-code records. Demographic information was harmonized across sources and linked to participant-level genotype data. ICD-9 and ICD-10 diagnosis codes were mapped to standardized PheCodes and further aggregated using hierarchical roll-up phenotypes to support broad phenotypic discovery. Quality control procedures included participant-level record harmonization, phenotype mapping verification, duplicate resolution, and minimum phenotype occurrence thresholds.

Results: The framework successfully integrated genomic, demographic, and EHR data for 149,691 unique participants (62.8% female, *n*=94,205; 37% male, *n*=55,347) and generated a comprehensive phenotype resource for downstream PheWAS analyses. ICD-based phenotyping produced approximately 20.3 million PheCode observations, which expanded to 28.5 million hierarchical phenotype observations following phenotype roll-up procedures. Application of a minimum occurrence threshold of two observations per participant yielded 11.0 million phenotype records suitable for association testing. APOE genotype distributions were consistent with those expected in a large population-based cohort, with E3/E3 as the predominant genotype (*n*=91,300; 61.0%), followed by E3/E4 (*n*=32,671; 21.8%), E2/E3 (*n*=18,485; 12.3%), E2/E4 (*n*=3,383; 2.3%), E4/E4 (*n*=2,800; 1.9%), and E2/E2 (*n*=1,027; 0.7%). Cohort age distributions reflected a predominantly middle-aged and older-adult population relevant for AD research.
Planned analyses will evaluate phenome-wide associations with *APOE* genotype, *APOE* ε4 allele dosage, and future Alzheimer's disease polygenic risk score models. These analyses aim to identify both established and potentially novel clinical phenotypes associated with genetic susceptibility to Alzheimer's disease.

Conclusions: We developed a scalable EHR-linked PheWAS framework that integrates genomic, demographic, and clinical data across nearly 150,000 participants. This resource establishes the foundation for systematic investigation of genetic risk of Alzheimer's disease and related dementias and supports future discovery of clinical correlates that may improve disease risk stratification, early detection, and precision medicine approaches

STUDENT POSTER # 147

EVALUATING THE IMPACT OF NETWORK SPARSIFICATION ON FUNCTIONAL CONNECTIVITY ANALYSIS IN ALZHEIMER'S DISEASE. Koyah K, Hughes D, Murzin E, Crook S. Arizona State University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is associated with progressive disruption of large-scale brain networks. Graph-theoretic analysis of resting-state functional magnetic resonance imaging (fMRI) is widely used to study alterations in brain network organization in AD. However, graph measures can be highly sensitive to how functional connectivity networks are constructed and sparsified. The impact of these methodological choices on observed AD-related network differences is not well understood. Different sparsification strategies may emphasize different aspects of network organization and lead to different conclusions, making it difficult to assess the robustness and reproducibility of reported findings.

Methods: Resting-state fMRI data from 20 AD individuals and 20 cognitively normal (CN) individuals obtained from the Alzheimer's Disease Neuroimaging Initiative were analyzed. Functional connectivity networks were constructed based on 96 brain regions using Pearson correlation of regional blood oxygen level-dependent time series. Three sparsification approaches were evaluated: single-absolute thresholding, multi-absolute thresholding analysis across a range of correlation cutoffs, and proportional thresholding with fixed network density. Global and regional graph measures, including clustering coefficient, participation coefficient, betweenness centrality, local efficiency, global efficiency, modularity, and small-worldness were computed. Relationships between network measures and Mini-Mental State Examination scores were also investigated. Ongoing work extends this framework using topological approaches that characterize network organization across continuous ranges of connectivity parameters.

Results: Global differences between AD and CN groups were modest and sensitive to sparsification choice. Multi-threshold analysis revealed apparent group differences that varied across thresholds, while proportional thresholding reduced many observed effects after controlling for network density. In contrast, regional analyses identified localized alterations in medial temporal, frontal, and parietal regions. Significant associations were observed between Mini-Mental State Examination scores and regional network measures, particularly within parahippocampal and prefrontal regions, suggesting links between cognitive performance and local network organization.

Conclusions: These findings demonstrate that sparsification choices influence graph-theoretic conclusions derived from functional connectivity networks. While global network differences between AD and CN groups were generally small, regional analyses revealed meaningful associations with cognitive performance. Ongoing work includes expansion to larger cohorts, machine learning approaches for classification, and exploration of topological data analysis methods as a complementary framework for identifying network structures that persist across multiple connectivity scales, to develop more robust and biologically meaningful biomarkers of Alzheimer's disease.

STUDENT POSTER # 148

BEYOND BPA: BPS EFFECTS ON THE AMYLOIDOGENIC PATHWAY IN DIFFERENTIATED SH-SY5Y NEURONAL CELLS AND THEIR RELATION TO ALZHEIMER'S DISEASE. Lang S, Mazo L, Vladich Z, Ashton NJ, Holechek S, Tseng H, Klein-Seetharaman J. Arizona State University; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease is a progressive neurodegenerative disorder characterized by beta-amyloid plaque accumulation, neurofibrillary tangles, and neuronal dysfunction. Its progression is influenced by genetic, environmental, and lifestyle factors. Bisphenol S (BPS), a common replacement for bisphenol A in plastics and resins, is structurally similar to estrogen and may act as an endocrine disruptor. Because estrogen signaling is involved in neuroprotective pathways, this study investigated whether BPS interferes with estrogen-related signaling and contributes to Alzheimer's disease-associated pathology in neuron-like cells.

Methods: Computational docking was used to compare predicted binding interactions of BPS and estradiol with estrogen-related targets and Alzheimer's-associated proteins. Modeling identified BACE1 as a target of interest. Human SH-SY5Y neuroblastoma cells were differentiated into neuron-like cells using retinoic acid and brain-derived neurotrophic factor. Estradiol concentrations were refined to physiologically relevant levels, including <10 pg/mL and 40 pg/mL, while BPS treatments were applied at environmentally relevant low and high concentrations of 1 ng/mL and 10 ng/mL. Cells were treated under varying BPS, estradiol, and inhibitor conditions to assess dose-dependent and competitive effects. Verubecestat, a BACE1 inhibitor, was included to evaluate whether BPS may influence amyloidogenic processing. Hydrogen-deuterium exchange immunoassays were used to assess phosphorylated tau and related protein biomarker changes, including p-tau 217, GFAP, and NfL.

Results: Initial results confirmed the qualitative presence of total tau, prompting further analysis of phosphorylated tau. HD-X analysis did not show a significant increase in phosphorylated tau following BPS exposure. Several biomarker levels, including p-tau 217, GFAP, and NfL, showed decreasing trends over time, which may reflect reduced cell viability or decreased protein secretion at later time points. These findings suggest that, under the conditions tested, BPS did not directly increase the phosphorylated tau markers analyzed.

Conclusions: The absence of a direct effect on phosphorylated tau does not rule out the possibility that BPS contributes to neurodegenerative risk through other mechanisms, nor does it dispute the possibility that BPS may be associated with dementia-related outcomes beyond Alzheimer's disease-specific tau pathology. Future work will focus on Western blot analysis to assess BACE1 expression across treatment conditions. Antibodies targeting components of the APP/BACE1 pathway will be used to determine whether BPS exposure alters amyloidogenic processing. Additional downstream markers, including sAPPbeta and Abeta42, may help clarify whether prolonged BPS exposure contributes to Alzheimer's disease risk through increased amyloidogenic signaling.

STUDENT POSTER # 149

DISSECTING THE ROLE OF MITOCHONDRIAL PATHWAYS ON ALZHEIMER'S DISEASE RISK AND RESILIENCE IN THE ROSMAP COHORT. Lee SM, Hussainy S, Liang J. University of Arizona; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia worldwide. Although its precise etiology remains unclear, AD is characterized by the accumulation of amyloid-beta plaques and neurofibrillary tangles. Notably, some individuals maintain normal cognitive function despite possessing substantial AD-related neuropathology, a phenomenon known as cognitive resilience (CR). The biological mechanisms underlying CR remain poorly understood.

Mitochondrial dysfunction, including disruptions in mitochondrial fission and fusion, is a well-established feature of AD and may contribute to both disease susceptibility and resilience. In this study, we investigated the genetic basis of CR to AD, with a particular focus on mitochondrial-related pathways. Using data from the Religious Orders Study and Memory and Aging Project (ROSMAP), we quantified CR, examined its relationship with AD polygenic risk, and evaluated associations between mitochondrial genes, mitochondrial pathways, AD risk, and resilience.

Methods: We analyzed data from 979 ROSMAP participants. CR was quantified using measures derived from ante-mortem cognition and post-mortem AD neuropathology. Associations between AD polygenic risk scores (PRS), AD-related traits, and CR were assessed using regression analyses. PrediXcan was used to estimate genetically regulated expression (GReX) for 61 mitochondrial-related genes, and associations with AD and CR were assessed across multiple brain regions. Gene Set Enrichment Analysis (GSEA) was performed to identify mitochondrial pathways associated with both outcomes.

Results: Higher AD PRS were associated with increased AD risk, greater neuropathological burden, poorer cognitive performance, and reduced CR. GReX analysis identified 13 mitochondrial-related genes associated with AD or CR. GPX1 showed the strongest signal and was consistently associated with increased AD risk and lower CR across multiple brain regions. Several genes involved in mitochondrial dynamics (OPA1, MFN2, DNM1L, MIEF1, and MFF) were significantly associated with CR. Fusion-related genes were positively associated with resilience, whereas fission-related genes were negatively associated with resilience. Pathway analyses further revealed significant enrichment of mitochondrial dynamic pathways for CR and antioxidant defense for AD diagnosis.

Conclusions: Our findings implicate mitochondrial dynamics as a key biological mechanism underlying CR to AD, enhanced mitochondrial fusion was associated with greater resilience, whereas increased mitochondrial fission was associated with increased vulnerability to cognitive decline. In addition, antioxidant defense pathways were associated with AD diagnosis, consistent with the established role of oxidative stress in AD pathogenesis. Together, these results highlight mitochondrial processes as potential therapeutic targets for promoting resilience and mitigating the impact of AD neuropathology.

STUDENT POSTER # 150

SINGLE-NUCLEUS PROFILING OF CELL-TYPE AND AGE-ASSOCIATED RETROTRANSPOSON EXPRESSION IN THE PRIMATE BRAIN. Leinenweber KE, Watkins KL, Mariner BL, Snyder-Mackler N. Arizona State University; Arizona Alzheimer's Consortium.

Background: Retrotransposons or retrotransposable elements (RTEs) are selfish DNA sequences that replicate through RNA intermediates and comprise approximately 45% of the primate genome. Mounting evidence suggests that although RTEs have evolved beneficial functions in the development and maintenance of the primate brain, their activity may contribute to neurodegeneration and neuroinflammation in older age. Despite the potential importance of RTEs, we still know very little about where and when they are expressed and how they interact with disease pathology. A better understanding of cell-specific and age-related RTE expression patterns across the healthy brain will help us discern where the boundary lies between healthy and deleterious RTE activity across the lifespan.

Methods: We used a single-nucleus RNA sequencing dataset containing 5.2 million cells across 11 brain regions from 55 rhesus macaques (N = 583 samples) to ask how RTE expression differs across cell types and across age.

Results: In our cell type analysis, we found that Alu elements, a family of short interspersed nuclear elements (SINEs), were more likely to be highly expressed in cerebellar neurons (OR = 61.4, $p < 0.01$), microglia (OR = 38.0, $p < 0.01$), vascular cells (OR = 24.8, $p < 0.01$), and basket cells (OR = 11.3, $p < 0.01$). This indicates that there are notable cell-type associated differences in RTE expression that are particularly pronounced for Alu elements.

Next, we evaluated age-related expression changes. RTE expression as a fraction of total transcripts comprised a large proportion (~35%) of the adult brain transcriptome and significantly increased with age across all cell types and most brain regions ($p < 0.05$). However, the nucleus accumbens, thalamus, and dorsolateral prefrontal cortex all showed a decrease in RTE expression with age ($p < 0.01$). We then tested how age affected the expression of individual RTEs and found several cell type and regional differences. In the cerebellum, 4.9% of all RTEs tested changed significantly with age, while less than 1% changed significantly in all other brain regions ($p < 0.05$). When grouped by cell type, 17.7% of RTEs tested in cerebellar neurons changed significantly with age, followed by 1.6% in basket cells, and less than 1% in all other cell types ($p < 0.05$). Cerebellar age changes were also specific to certain RTE classes, with long interspersed nuclear elements (LINEs) and long terminal repeat elements (LTRs) predominantly downregulated (OR = 0.4 and 0.9, respectively; $p < 0.01$) and SINEs predominantly upregulated (OR = 10.4, $p < 0.01$) with age. This pattern was not observed in other brain regions, indicating that there are regional differences in age-related RTE expression changes, particularly in the cerebellum.

Conclusions: Given that RTEs contribute to both essential brain function and age-related decline, this analysis explores where and when RTEs are expressed, and what that means biologically. We identified Alu elements and the cerebellum as particular areas of interest in the role that RTEs play in brain aging. Together, these results advance our understanding of RTE activity in the brain across the lifespan, shedding light on how these patterns differ across diverse cell types and brain regions.

STUDENT POSTER # 151

GENERATION AND VALIDATION OF ISOGENIC BIN1 KNOCKOUT AND BIN1 P381L HUMAN INDUCED PLURIPOTENT STEM CELL MODELS TO INVESTIGATE ALZHEIMER'S DISEASE RISK MECHANISMS. Leyasi S, Hyun F, Brafman D. Arizona State University; Arizona Alzheimer's Consortium.

Background: Late-onset-Alzheimer's disease (LOAD) is a multifactorial neurodegenerative disease that is influenced by numerous genetic factors. Multiple genome wide association studies and meta-analysis have identified Bridger Integrator 1 gene (BIN1) as risk locus for LOAD, second to that of APOE. BIN1 is a ubiquitous protein involved in membrane remodeling and is a regulator of intracellular trafficking. Despite BIN1's strong association with AD, the normal biological function of BIN1 in human neurons and its mechanistic contribution to disease remain poorly understood. It remains unclear whether BIN1 dysfunction initiates downstream alterations in amyloid precursor protein (APP) processing, endolysosomal homeostasis, and tau pathology that contribute to neurodegeneration. We have developed clonal isogenic human induced pluripotent stem cell (hiPSC) lines to model to establish a genotype-to-phenotype connection between BIN1 and Alzheimer's disease (AD) pathology. This platform enables the investigation of BIN1's impact on AD pathologies and effect on cell specific phenotypes.

Methods: We used prime-induced nucleotide engineering using a transient reporter for editing enrichment (PINE-TREE) to generating clonal isogenic lines for BIN1 knockout and the P318L mutation in hiPSCs. The PINE-TREE system utilizes CRISPR/CAS9 genome engineering with a transient fluorescent reporter that converts blue-fluorescent-protein (BFP) to green-fluorescent protein (GFP) upon the presence of necessary prime editing machinery. Single cell clones were sorted based on dual GFP/BFP expression and screened for the presence of the intended genomic edit. Edited clones were validated for on- and off-target editing, expression of pluripotency markers, spontaneous trilineage differentiation, and a normal euploid karyotype. Loss of BIN1 expression was confirmed through Western Blot.

Results: WT, BIN1KO, and BIN1P318L lines were successfully differentiated into disease-relevant neural lineages enabling investigation of BIN1-dependent cellular phenotypes associated with AD risk. Ongoing analyses focus on evaluating loss of BIN1 expression on key pathways implicated in AD, including endocytic trafficking, synaptic activity, and neuronal function.

Conclusions: The established WT, BIN1KO, and BIN1P318L hiPSC lines establishes a controlled platform to establish a genotype to phenotype relationship between BIN1 variants and AD, while minimizing variability due to genetic background. These lines establish a human-based preclinical model to dissect the functional consequences of AD risk mutations and provide a versatile framework for therapeutic discovery by enabling testing of candidate therapies, or biomaterials designed to restore normal BIN1 function or counteract its downstream effects. Additionally, the TREE system can be further used to model other identified BIN1 AD risk mutations in hiPSCs (BIN1K358R and rs744373). This platform can be applied further to dissect the relationship between specific BIN1 AD risk variants and their effects in AD pathology.

STUDENT POSTER # 152

NNMOBILENET++: AN EFFICIENT HYBRID CNN-TRANSFORMER FRAMEWORK FOR RETINAL IMAGE ANALYSIS. Li X, Zhu W, Dong X, Wang H, Xiong Y, Dumitrascu O, Wang Y. Arizona State University; Mayo Clinic Arizona; Clemson University; Arizona Alzheimer's Consortium.

Background: Retinal imaging provides a non-invasive and cost-effective approach for the detection of both ocular and neurodegenerative diseases. Although convolutional neural networks (CNNs) have demonstrated strong performance in retinal image analysis, their reliance on local convolution operations limits the modeling of long-range dependencies and complex vascular structures. This limitation is particularly relevant because retinal vascular features are important biomarkers for neurodegenerative diseases such as Alzheimer's disease (AD). To address these challenges, we developed nnMobileNet++, a lightweight hybrid CNN–Transformer framework incorporating Dynamic Snake Convolution (DSC), transformer-based global context modeling, and retinal-specific self-supervised pretraining.

Methods: We developed nnMobileNet++, a lightweight hybrid CNN–Transformer framework for retinal image analysis. The framework incorporates Dynamic Snake Convolution (DSC) to better preserve vascular structures, transformer modules to capture long-range dependencies, and retinal-specific self-supervised pretraining using SimMIM. The model was pretrained on 114,275 gradable retinal fundus photographs from the UK Biobank and subsequently evaluated on multiple public retinal image datasets, including MuReD, ODIR, MMAC 2023, UWF4DR 2024, and MuCaRD 2025. Model performance was assessed using area under the receiver operating characteristic curve (AUC), F1 score, accuracy, and area under the precision–recall curve (AUPRC), depending on the task.

Results: Across all evaluated datasets, nnMobileNet++ consistently outperformed conventional CNN and Vision Transformer baselines. On the MuReD multi-label retinal disease dataset, nnMobileNet++ achieved an AUC of 0.842, F1 score of 0.445, and AUPRC of 0.398 following retinal-specific self-supervised pretraining. On the ODIR dataset, the framework achieved an AUC of 0.906 and F1 score of 0.494. nnMobileNet++ also demonstrated strong performance on multiple MICCAI challenge benchmarks, achieving an AUC/F1 of 0.946/0.746 on MMAC 2023, 0.893/0.867 for diabetic macular edema detection on UWF4DR 2024, and 0.739/0.669 on MuCaRD 2025. Ablation studies further confirmed that both DSC and transformer modules contributed to performance improvements while maintaining a lightweight architecture.

Conclusions: nnMobileNet++ provides an efficient and robust framework for retinal image analysis by improving the representation of vascular and lesion-related features. The model demonstrated strong generalizability across diverse retinal imaging datasets while maintaining low computational complexity. Given the growing interest in retinal biomarkers for neurodegenerative disorders, improved characterization of retinal vascular structures may support future retinal biomarker research in neurodegenerative diseases.

STUDENT POSTER # 153

RETINALGPT: INSTRUCTION-TUNED VISION–LANGUAGE INTELLIGENCE FOR RETINAL BIOMARKERS OF ALZHEIMER'S DISEASE. Li X, Zhu W, Su Y, Huentelman M, Wang Y, Dumitrascu O. Arizona State University; Banner Alzheimer's Institute; Translational Genomics Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Current Multimodal Large Language Models (MLLMs) such as LLaVA-Med, lack the specialized capability for quantitative retinal vascular assessment required in clinical ophthalmology. Specifically, they fail to measure fine-grained metrics like vessel density and fractal dimensions, which are critical for diagnosing Diabetic Retinopathy (DR) or identifying retinal biomarkers for Alzheimer's Disease (AD). This study aims to bridge this gap by introducing a specialized assistant designed for the quantitative analysis and interpretation of color fundus photographs (CFPs).

Methods: To achieve precise retinal pathology understanding, we constructed a conversational AI framework comprising three core components: (1) the compilation of a large-scale, high-quality CFP dataset; (2) the automated morphological quantification pipeline; and (3) the implementation of customized visual instruction tuning. This tuning strategy was specifically designed to align the model's visual perception with expert medical knowledge, enabling it to perform complex tasks ranging from ophthalmic disease and AD classification, fine-grained localization of specific lesions such as hemorrhages and exudates and automated retinal fractal analyses.

Results: Extensive evaluations on eight benchmark datasets of CFPs demonstrate that our proposed assistant outperforms state-of-the-art general-domain MLLMs by a significant margin in ophthalmic diseases and AD classification. Beyond binary diagnosis, the model successfully performs lesion localization (e.g., hemorrhages and exudates) and quantitative vascular analyses (e.g., fractal dimension) that correspond with clinical standards. The results validate the model's ability to provide interpretable, end-to-end reasoning for both ophthalmic and systemic diseases biomarker discovery (fractal dimension).

Conclusions: By integrating quantitative vascular analysis with conversational AI, our assistant offers an interpretable framework for clinical ophthalmology. This work establishes a new paradigm for human-AI collaboration in ophthalmic diagnostic interpretation and retinal biomarker of systemic diseases discovery.

STUDENT POSTER # 154

FEASIBILITY AND ACCEPTABILITY OF AT-HOME PTAU217 COLLECTION USING CAPITAINER® SEP10 DRIED PLASMA SPOT CARDS AMONG MEXICAN-ORIGIN ADULTS.

Lindemer SL, Felix M, Gomez A, Ashton NJ, Maldonado A, Huentelman M, Chen N, Aguiñaga S, Rodriguez M, Garcia DO. University of Arizona; Banner Sun Health Research Institute; Translational Genomics Research Institute; University of Illinois Urbana - Champaign; Arizona Alzheimer's Consortium.

Background: Blood-based biomarkers, including phosphorylated tau at position 217 (pTau217), are transforming Alzheimer's disease detection and research. However, venipuncture-based collection may limit participation among underserved populations due to barriers related to transportation, scheduling, and healthcare access. Remote blood collection technologies, such as Capitainer® SEP10 dried plasma spot cards, may provide a scalable alternative for community-based biomarker collection. As part of an AAC pilot study, we evaluated the feasibility and acceptability of at-home pTau217 collection among Mexican-origin (MO) adults.

Methods: MO adults enrolled in a community-based cognitive health study completed pTau217 collection using Capitainer® SEP10 dried plasma spot cards at three time points: staff-assisted baseline collection, at-home self-collection using a take-home kit with mailing instructions, and staff-assisted collection during a follow-up visit. Feasibility outcomes included collection completion and at-home sample return. A participant experience survey assessed ease of use, confidence with self-collection, perceived barriers, satisfaction, and willingness to participate in future biomarker studies on a five-point Likert scale (5 being the highest positive score).

Results: Among 40 MO adults, the mean age was 58.9 ± 3.9 years, mean BMI was 30.1 ± 6.3 kg/m2, and 35 participants (87.5%) were female. Staff-assisted collections were completed by all participants at baseline and follow-up (40/40; 100%). At-home collection was completed by 34 participants (85.0%); 4 (10%) reported completing the mailing, but this could not be verified; and 2 (5%) did not complete self-collection. Participant experience surveys indicated high acceptability, including ease of use (4.28 ± 1.22), confidence completing the collection (4.10 ± 1.34), satisfaction with participation (4.78 ± 0.80), and willingness to participate in future studies (4.75 ± 0.81). Common challenges included concerns about performing the finger-stick correctly, uncertainty about sample adequacy, and the need for additional instruction or support.

Conclusions: The use of Capitainer® SEP10 dried plasma spot cards is feasible and acceptable for collecting pTau217 samples among MO adults in community-based AD research. Remote blood spot collection may help expand access to biomarker testing and increase participation in aging research among underserved populations. Findings will inform future implementation of blood-based biomarker collection strategies in community and clinical settings.

STUDENT POSTER # 155

BETWEEN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE AND COGNITIVE FUNCTION AMONG MEXICAN-ORIGIN ADULTS. Lindemer SL, Felix M, Gomez A, Maldonado A, Huentelman M, Chen N, Aguiñaga S, Rodriguez M, Butler D, Garcia DO. University of Arizona; Translational Genomics Research Institute; University of Illinois Urbana - Champaign; Georgetown University; Arizona Alzheimer's Consortium.

Background: Mexican-origin (MO) adults experience disproportionately high rates of metabolic dysfunction-associated steatotic liver disease (MASLD), mild cognitive impairment (MCI), and Alzheimer's disease (AD) risk factors, yet remain underrepresented in cognitive aging research. This study examined associations between MASLD and cognitive function among MO adults in Southern Arizona.

Methods: Participants were recruited through Nosotros Comprometidos a Su Salud and completed FibroScan® and neuropsychological testing as part of an Arizona Alzheimer's Consortium pilot study. MASLD was defined as FibroScan® controlled attenuation parameter (CAP) ≥288 dB/m. Cognitive outcomes included global cognition (MoCA-S), executive function/processing speed (Trail Making Test A/B, Stroop Color and Color-Word, verbal fluency, Symbol Digit Modalities Test), working memory (Digit Span Forward/Backward, Digit Ordering), and episodic memory (Logical Memory I/II). Cognitive tests were z-standardized and averaged into domain-level composite scores, with Trail Making Test A/B reverse-scored so higher scores indicated better performance. Multivariable linear regression models examined associations between MASLD status and cognition, adjusting for age, sex, BMI, and depressive symptoms. Secondary models examined liver steatosis and fibrosis as continuous predictors.

Results: Forty-three MO adults enrolled in the study. Mean age was 58.8 ± 3.8 years, mean BMI was 30.1 ± 6.1 kg/m², and 37 participants (86.0%) were female. Eleven participants (25.6%) met criteria for MASLD. Mean liver steatosis was 262.5 ± 47.8 dB/m, and mean fibrosis was 4.9 ± 2.5 kPa. In adjusted models, MASLD status was associated with lower global cognition/MoCA-S performance (β = -3.10, SE = 1.39, 95% CI: -5.93, -0.26; p = 0.034), but not with executive function/processing speed, working memory, episodic memory, or the overall cognitive composite. Higher CAP scores were associated with lower global cognition (β = -0.028, p = 0.055) and Digit Ordering performance (β = -0.015, p = 0.089). Fibrosis was not significantly associated with cognitive outcomes.

Conclusions: Among MO adults, MASLD was associated with lower global cognitive performance after adjustment for covariates. Although MASLD was not associated with domain-level cognitive composites, higher liver steatosis showed trends toward poorer global cognition and working memory. Larger, longitudinal studies are needed to clarify whether reducing liver steatosis may help preserve cognitive health in this underserved population.

STUDENT POSTER # 156

THE COGNITIVE EFFECTS OF NONHORMONAL MENOPAUSAL THERAPY DEPEND ON THE PRESENCE OF REPRODUCTIVE TRACT ORGANS: EXPLORING THE NEW HORIZON OF VASOMOTOR THERAPIES. Lizik CR, Anyigbo KJ, Wu ES, Oevermann MW, Doyle RT, Kalas SA, Garayzar Lopez A, Gonzalez-Cruz I, Hannahs MK, Kaur I, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.

Background: Within the last several years, new nonhormonal pharmacotherapies targeting the neurokinin (NK) system have been developed for the treatment of menopausal-associated vasomotor symptoms (VMS), which include hot flashes and night sweats. The NK system plays a role in thermoregulation, and NKR antagonists are considered a safe alternative to hormonal formulations often used for menopausal therapy. The implications of NKR antagonism on cognition are not well understood, but are especially relevant considering that the majority of users are menopausal women, who are at increased risk for the development of Alzheimer's disease (AD). Moreover, approximately half of women experience gynecological surgery with reproductive tract organ removal in their lifetime, highlighting the need to understand the effects of a range of menopausal therapies on gynecological tract variants.

Methods: Here, we used a rodent model to evaluate the impact of Fezolinetant (Fez), a recently approved NKR antagonist used for VMS, on cognition across several models of gynecological surgery: Ovariectomy (removal of the ovaries with uterine retention, Ovx) and Hysterectomy (removal of the uterus with ovarian retention, Hyst), as well as in sham-operated controls.

Results: Fez improved memory performance in sham-operated, reproductively-intact rodents, an effect not seen when any part of the reproductive tract was removed.

Conclusions: This is the first report suggesting that Fez improves memory, and that this mnemonic functional impact is altered by gynecological surgery. These outcomes have far-reaching implications; indeed, as evidence is accumulating, our understanding is evolving and supporting the tenet that menopause is not a singular process or physiological event. There are distinct variations in how individuals experience menopause, underscoring the importance of individualized medicine, including varied evaluative and therapeutic approaches. This study, combined with evidence that less than 3% of neuroscience research is devoted to women's health-related factors, underscores the critical need to further investigate how menopause therapies impact multi-systems health, especially when mapped onto varied backgrounds of menopause and reproductive tract status. More focus in this research domain is needed so that targeted, personalized therapeutic strategies for menopause can be developed to optimize brain health during aging in women and gender-nonconforming individuals

STUDENT POSTER # 157

TREADMILL-BASED TASK FOR ASSESSING NEURAL CORRELATES OF TIME ESTIMATION ACROSS MULTIPLE DURATIONS AND CONTEXTS IN THE TGF344-AD RAT MODEL OF ALZHEIMER'S DISEASE. Maillard S, Dougherty R, Pederson V, Roemer G, Sweet E, Cowen SL. University of Arizona; Arizona Alzheimer's Consortium.

Background: Time perception is a critical faculty impacted by Alzheimer's disease (AD) and is a key feature assessed by clinicians in diagnosis. Despite this, much remains unknown about the neural bases of impaired time perception in AD. Research using rodent models of AD has begun to elucidate mechanisms through which hippocampal circuitry involved in episodic and contextual memory are disrupted, but the relationship between these mechanisms and those underlying deficits in time estimation is still unclear. Here, we developed a task for investigating the neural correlates of time estimation in wildtype (WT) and TgF344-AD rats, a rat model of AD which recapitulates key pathological hallmarks such as age-dependent accumulation of amyloid plaques and tau pathology.

Methods: This preliminary study included 3 female transgenic rats (12-13 mo.) comprised of both TgF344-AD (n = 1) and WT control (n = 2) animals. Rats were trained to perform a time estimation task where they were required to walk on a moving treadmill. The treadmill stopped for a rest period of 20-40 seconds if the animals nose-poked a port at the end of the treadmill after (but not before) a pre-specified interval of 5 or 10 s. Nose-pokes before the specified interval were penalized by increasing the treadmill speed and the length of the trial. To aid training, an auditory tone initially signaled the end of the interval. The portion of tone-cued trials was decreased as rats approached asymptotic performance. Intervals were presented in blocks of 20 trials in an A-B-A order (i.e., Block A: 20 trials at 5 s, Block B: 20 trials at 10 s, etc.) and were associated with distinct olfactory/visual contexts which the rat could use to discriminate the delay interval.

Results: Results indicated that rats were able to successfully acquire the time estimation behavior, reaching >80% accuracy (mean accuracy = 87.04 ± 5.94%) across intervals and significantly discriminating between 5 and 10 s blocks (A1 vs. B: mean Cohen's d = -1.96 ± 0.39; B vs. A2: mean Cohen's d = 2.18 ± 0.33).

Conclusions: These preliminary results suggest that this treadmill-based task provides a paradigm for evaluating neural mechanisms of interval timing in TgF344-AD rats. Next steps include implementing high-density electrophysiological recordings to investigate hippocampal population dynamics in AD and WT rats performing the time estimation behavior.

STUDENT POSTER # 158

THE IMPACT OF TRAUMA EXPOSURE ON THE RELATIONSHIP BETWEEN COGNITIVE FLEXIBILITY AND EMOTIONAL CLARITY IN OLDER WOMEN. Marshall A, Huggins A, Huynh N, Terner J, Barlis K. University of Arizona; Arizona Alzheimer's Consortium.

Background: Emotion dysregulation is a multi-dimensional cluster of symptomologies common in trauma-related psychopathology. One aspect of emotion regulation is emotional clarity, which is the extent to which an individual is aware of and can understand their emotions. Effective emotion regulation depends on higher level executive functioning, especially processes like cognitive flexibility which has been shown to decline with age. In this project we investigate whether trauma exposure in various forms of origin and levels of accumulation disrupt the relationship between cognitive flexibility and emotional clarity in older women.

Methods: Older (60+ years old) biologically female adults (n= 39) completed a standardized neuropsychological test battery and self-report questionnaires, including the Lifetime Events Checklist (LEC-5), Difficulties in Emotion Regulation Scale (DERS-16), Community Experiences Questionnaire (CEQ), and Childhood Trauma Questionnaire (CTQ). Trauma scores for analysis were obtained from subdomains of each scale pertaining to physically and sexually violent events. Cognitive flexibility scores were operationalized as the sum of norm-scored Delis-Kapan Executive Functioning System (DKEFS) Trail-Making and Color-Word Interference tasks. Lack of emotional clarity subdomain scores from the DERS-16 were used as the outcome variable. Moderated linear regression models tested the effect of community violence via direct victimization versus witness, childhood trauma, and reports of traumatic life events on cognitive flexibility.

Results: The interaction between direct victimization of community violence and cognitive flexibility significantly affected self-reported difficulties in emotional clarity ($b = 0.25$, $p = 0.052$). This effect did not emerge for witnessed community violence. Additionally, direct exposure to violent life events reported on the LEC-5, including physical assaults, sexual assaults, combat, and captivity, significantly moderated this relationship ($b = 0.105$, $p = 0.040$). Violent childhood trauma, defined as sexual or physical assault occurring before age 18, also showed a significant moderating effect ($b = 0.103$, $p = 0.015$). However, total childhood trauma across all CTQ categories and the cumulative effects of all traumatic life events reported on the LEC-5 (including natural disasters and work/transportation accidents) did not demonstrate significant moderating effects on this relationship.

Conclusions: The experience of violent traumas, whether classified as community violence, physical assault, or sexual assault, had a significant moderating effect on self-reported difficulties in emotional clarity among older women. This moderating effect persisted for both childhood trauma and cumulative lifetime trauma. These findings suggest that different forms of traumatic experiences may have distinct effects on emotional wellbeing.

STUDENT POSTER # 159

INDUCIBLE NITRIC OXIDE SYNTHASE UNDERLIES BKCA CHANNEL DYSFUNCTION AND MICROVASCULAR DEFICITS IN FEMALE 5X-FAD MICE. Martin PE, Polk FD, Vikram Aditya R, Cornell T, Pires PW. University of Arizona; Arizona Alzheimer's Consortium.

Background: Neurovascular dysfunction occurs early in Alzheimer's disease (AD) and may contribute to disease progression and severity. Previous work from our laboratory showed that cerebral arteries of 5x-FAD mice are hypercontractile due to reduced activity of large conductance, calcium-activated potassium channels (BKCa), which was associated with blunted neurovascular coupling responses. In female mice, this was due to exacerbated S-nitrosylation of the channel resulting from expression of inducible nitric oxide synthase (iNOS, gene Nos2). In the pro-oxidative environment of the AD brain, iNOS-dependent uncontrolled nitric oxide (NO) production may result in accumulation of peroxynitrite, a strong oxidant. We hypothesize that increased iNOS expression leads to BKCa dysfunction due to nitro-oxidation of the channel, resulting in cerebral vascular hypercontractility in female 5x-FAD mice.

Methods: Eight-month-old female 5x-FAD, 5x-FAD:Nos2+/-, and wild-type (WT) mice were used. Prior to euthanasia, cerebral blood flow recordings, to assess neurovascular coupling, were performed in vivo. Pial arteries were then isolated and either canulated for pressure myography or underwent a mild enzymatic digestion to isolate smooth muscle cells for patch clamp electrophysiology.

Results: BKCa channel activity, assessed via single-channel and perforated patch clamp electrophysiology, was lower in 5x-FAD than in WT, but was recovered in 5x-FAD:Nos2+/- mice. Although spontaneous myogenic tone of pressurized pial arteries was not different between 5x-FAD and 5x-FAD: Nos2+/- mice, vasoconstriction after BKCa blockade with iberiotoxin (300 nM), was larger in 5x-FAD: Nos2+/- mice, suggesting improved BKCa basal activity. Dithiothreitol (DTT, 10 μM), a potent reducing agent, increased pial artery constriction to iberiotoxin in 5x-FAD but had no additive effects in 5x-FAD: Nos2+/- mice, suggesting that removal of one copy of the Nos2 gene partially reduces nitro-oxidation of the channel. The 5x-FAD: Nos2+/- mice had an improved neurovascular coupling response in vivo compared to 5x-FAD mice via laser speckle contrast imaging.

Conclusions: In summary, our data show iNOS expression underlies BKCa dysfunction in cerebral arteries of female 5x-FAD mice. Our findings are the first to identify iNOS as a central mechanism of microvascular deficits in AD mice and a potential therapeutic target to improve cerebral vascular function in AD.

STUDENT POSTER # 160

AGING ALTERS BRAIN RECOVERY TRAJECTORIES FOLLOWING SYSTEMIC ESCHERICHIA COLI INFECTION. Massa N, Todd K, Cadiz M, Haug K, Nascari D, Barnett J, Fryer JD. Mayo Clinic Arizona; Translational Genomics Research Institute; Alzheimer's Consortium.

Background: Sepsis is a major cause of mortality and long-term cognitive impairment, particularly in older adults. Aging is associated with an increased risk of sepsis-associated encephalopathy (SAE) and poor neurological outcomes, yet the mechanisms underlying age-dependent differences in brain responses following infection remain poorly understood. This study investigated how aging influences molecular and cellular responses in the brain during recovery from systemic Escherichia coli infection.

Methods: Young (3-month-old) and aged (15–17-month-old) C57BL/6 mice were subjected to intraperitoneal E. coli infection followed by antibiotic treatment. Brain tissue was collected at early (2 days) and late (21 days) post-infection timepoints. Bulk RNA sequencing was performed to characterize global transcriptional changes, while single-cell RNA sequencing was used to identify cell type-specific responses. Immunofluorescence staining is ongoing to evaluate age- and infection-related changes in microglia, neurons, astrocytes, and endothelial cells within the hippocampus and cortex.

Results: Bulk RNA sequencing revealed baseline transcriptional differences in aged brains characterized by enrichment of immune and inflammatory pathways alongside reduced neuronal-associated gene expression. Following infection, both young and aged mice mounted robust early transcriptional responses; however, aged mice exhibited enhanced inflammatory, myeloid, and vascular-associated programs compared to young mice. By 21 days post-infection, responses diverged markedly by age. Young mice exhibited sustained transcriptional remodeling involving translation, metabolism, immune signaling, and structural remodeling pathways, whereas aged mice displayed limited differential gene expression and reduced pathway enrichment, indicative of a restricted late response. Single-cell RNA sequencing identified microglia and endothelial cells as major contributors to these age-dependent differences. At baseline, aged microglia exhibited inflammatory priming, while aged endothelial cells displayed stress-responsive and structurally vulnerable transcriptional states. Following infection, young microglia and endothelial cells underwent broad and coordinated transcriptional remodeling, whereas aged cells exhibited more limited and less coordinated responses, particularly at the late timepoint. Consistent with these molecular findings, aged mice demonstrated impaired physiological recovery, including sustained weight loss following infection.

Conclusions: These findings demonstrate that aging fundamentally alters the trajectory of brain responses following systemic infection, shifting the response from coordinated recovery-associated remodeling in young mice to a restricted and potentially dysregulated response in aged mice. Age-related alterations in microglial and endothelial cell responses may contribute to impaired recovery and increased susceptibility to persistent neurological dysfunction following infection.

STUDENT POSTER # 161

RELIABILITY OVER SENSITIVITY: COMPARING FULLY AUTOMATED AND ULTRA-SENSITIVE IMMUNOASSAY FOR PTAU217. Mazo LM, Singh A, Denkinger MN, Liu J, Dieckhoff K, Marques TM, Wilson R, Reyes R, Leuzy A, Ghisays V, Head E, Beach TG, Serrano G, Atri A, Reiman, EM, Langbaum JB, Johnson SC, Ashton NJ. Banner Sun Health Research Institute; Arizona State University; University of Wisconsin, Madison; The Michael J Fox Foundation, Gothenburg, Sweden; Banner Alzheimer's Institute; UC Irvine Center for the Neurobiology of Learning and Memory; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) pathology, characterized by amyloid-β and tau accumulation, begins decades before clinical symptoms, creating a need for reliable blood-based biomarkers capable of detecting disease at its earliest stages. Plasma phosphorylated tau at threonine 217 (p-tau217) has emerged as a promising biomarker for identifying AD pathology, with initial validation largely performed using ultra-sensitive research platforms such as the Simoa HD-X. As biomarker testing moves toward large-scale clinical implementation, there is increasing demand for fully automated clinical analyzers offering scalability, standardization, and accessibility. P-tau217 concentrations are lower in cognitively unimpaired (CU) individuals, raising uncertainty about whether automated clinical platforms provide comparable analytical sensitivity and diagnostic accuracy for detecting early biomarker changes. This study compared plasma p-tau217 performance between the Quanterix HD-X Simoa research platform and Roche cobas e801 automated clinical analyzer for detecting amyloid pathology in cognitively unimpaired individuals.

Methods: Participants were drawn from the Wisconsin Registry for Alzheimer's Prevention (WRAP), a longitudinal cohort enriched for preclinical AD. This interim analysis included 670 participants with amyloid-PET imaging and plasma p-tau217 measurements. Amyloid burden was quantified using Centiloid values, with positivity thresholds of >12.1, >18.1, and >24.1. Plasma p-tau217 was measured on both platforms. Analyses assessed discrimination of amyloid-PET positivity, agreement between platforms, and biomarker associations.

Results: Participants had a mean age of 68.9 ± 7.6 years, 68.2% were female, and most were cognitively unimpaired. Plasma p-tau217 differed by amyloid status across both platforms. ROC analysis showed consistently stronger discrimination for Roche versus HD-X across all thresholds. At >12.1, >18.1, and >24.1 Centiloids, Roche achieved AUCs of 0.89 (95% CI: 0.86-0.91), 0.93 (0.91-0.95), and 0.94 (0.92- 0.96), compared with HD-X AUCs of 0.82 (0.79-0.86), 0.87 (0.84-0.90), and 0.89 (0.86-0.92), indicating improved classification accuracy. Measurements showed a significant mean difference of 0.194 pg/mL (SD = 0.155; $p < 0.0001$), with Roche values consistently higher. The estimate was precise (95% CI: 0.190-0.198; SEM = 0.00218). Despite strong correlation ($r = 0.88$, $p < 0.0001$), the magnitude of difference indicates the methods are not interchangeable.

Conclusions: Plasma p-tau217 showed robust performance for detecting early AD pathology across both platforms, supporting its utility as a scalable biomarker for preclinical disease. Roche cobas e801 showed superior discrimination of amyloid positivity versus Quanterix HD-X, demonstrating that high-throughput automated analyzers can achieve comparable or improved performance in predominantly CU populations where biomarker concentrations are lowest. These findings support translation of blood-based AD biomarkers into routine clinical practice. However, systematic platform differences highlight the need for assay-specific thresholds, standardization, and cross-platform harmonization. Accurate, scalable automated biomarker testing could enable population-level screening, improve early patient identification, and accelerate recruitment into AD prevention trials.

STUDENT POSTER # 162

SINGLE-NUCLEI TRANSCRIPTOMICS IDENTIFIES CELL-TYPE-SPECIFIC ESTROGEN-DEPENDENT PATHWAY ALTERATIONS RELEVANT TO ALZHEIMER'S DISEASE IN FEMALE RAT HIPPOCAMPUS. McLean JW, Wang T, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.

Background: Estrogen regulates metabolic, immune, and neuronal function in the female brain. Reduction in estrogen levels during menopause impacts processes associated with Alzheimer's disease (AD) pathogenesis, including glucose utilization, mitochondrial function, and neuroinflammation, likely contributing to the doubled female lifetime risk for AD. However, the cell-type-specific response to estrogen deficiency in the hippocampus, which is critically affected in AD, is insufficiently understood.

Methods: To elucidate hippocampal cells and pathways affected by estrogen loss, 5-month-old female Sprague Dawley rats were assigned to sham ovariectomized (SHAM), ovariectomized plus vehicle (OVX), or OVX with 17-beta-estradiol (OVX+E2) conditions and sacrificed 5 weeks post-surgery. Single nuclei were isolated from dorsal hippocampus, pooled across two biological replicates per group, and processed using the 10X Genomics Chromium Single Cell 3' platform. Libraries were sequenced on an Illumina NovaSeq6000, and downstream analyses were conducted using CellRanger v9.0.1 and R v4.5.2. Following quality control filtering out nuclei with >5% mitochondrial reads, canonical marker genes were used to annotate major brain cell types. Cell-type proportion tests, differential expression, pathway-level analyses, and CellChat ligand-receptor (LR) interaction tests were performed across conditions and cell types.

Results: Relative to SHAM, OVX shifted cellular composition toward reduced excitatory (Exc) and inhibitory (Inh) neuron and elevated oligodendrocyte (Olig) proportions. Pathway analysis of DEG's between OVX and SHAM indicated significantly enriched KEGG pathways associated with neurodegeneration (Exc) and inflammation (Exc, Inh, Olig), while metabolic pathways were downregulated (Olig). Neuroactive ligand signaling was also significantly diminished in multiple OVX cell types, prompting an LR interaction analysis using CellChat. This indicated a specific deficit in predicted OVX Exc communication toward both Exc and Inh along with elevated microglial signaling with Inh and Olig. OVX+E2 partially mitigated several OVX-induced phenotypes, including cell-type composition shifts, Inh inflammatory response, and both Exc-Exc and Exc-Inh communication predicted via CellChat.

Conclusions: These findings extend previous reports connecting estrogen loss to AD risk by identifying cell-type-specific metabolic, inflammatory, and cell signaling phenotypes induced by OVX and partially moderated by E2 replacement. Ongoing analyses will further resolve cell-type-specific ligand-receptor interactions underlying estrogen-dependent vulnerability to AD.

STUDENT POSTER # 163

PROBING PATHOLOGICAL MECHANISMS IN HUMAN IPSC-DERIVED DOPAMINE NEURONS FROM INDIVIDUALS WITH SPORADIC PARKINSON'S DISEASE. McRobbie-Johnson A, Bernard K, Corenblum MJ, Tonino P, Langlais P, Madhavan L. University of Arizona; Arizona Alzheimer's Consortium.

Background: A major roadblock impeding the development of effective therapeutics for Parkinson's disease (PD) has been the inadequate understanding of its etiopathology. From this perspective, we studied several induced pluripotent stem cell (iPSC)-derived dopamine neuron (iPSC-DAN) lines, from individuals with idiopathic PD, that constitutes more than 90% of PD cases.

Methods: Sporadic PD (n=10) and age- and sex-matched controls (n=10) iPSC lines were differentiated into dopamine neurons (iPSC-DAN) for 50-55 days via a modified floor plate-based method using dual SMAD inhibition. Bioenergetic function was assessed using Seahorse assays to measure oxidative phosphorylation and glycolysis, while mitochondrial dynamics, membrane potential, and creatine kinase localization were evaluated to examine mitochondrial homeostasis. Cellular viability and oxidative stress were measured using MTT and DCFH-DA assays, respectively. α-synuclein localization was analyzed by immuno-electron microscopy, and total as well as phosphorylated (Ser129) α-synuclein levels were quantified using western blotting.

Results: Across these various analyses, PD neurons exhibited broad metabolic impairments characterized by reduced oxidative phosphorylation (OXPHOS) capacity (including basal and maximal respiration, and ATP production), diminished glycolytic reserve and altered creatine kinase localization indicating compromised metabolic function. Mitochondrial fission/fusion and mitophagy dynamics, and mitochondrial membrane potential, were also compromised in the PD neurons. These bioenergetic deficits were accompanied by reduced cellular viability and increased oxidative stress. Moreover, an increased mitochondrial association of α-synuclein (α-syn), a protein known to play a key role in PD, was observed via immuno-electron microscopy. Consistent with these findings, elevated levels of total and phosphorylated (Ser129) α-synuclein (pα-syn) were detected. When separated by sex, male-derived PD neurons exhibited more pronounced mitochondrial dysfunction, reduced OXPHOS, higher pα-syn, whereas the female-derived neurons showed comparatively milder bioenergetic impairments and more monomeric α-syn.

Conclusions: Collectively, these findings demonstrate that idiopathic PD iPSC-DAN recapitulate an interconnected network of impaired mitochondrial and proteostatic homeostasis, and α-syn pathology, with sex-specific differences that may influence disease severity and progression.

STUDENT POSTER # 164

FINE MOTOR IMPAIRMENTS EMERGE PRIOR TO COGNITIVE DYSFUNCTION AND PERSIST THROUGHOUT LIFE IN THE TGF344-AD RAT MODEL OF ALZHEIMER'S DISEASE. Melick AM, Christiansen K, Krishnan T, Bimonte-Nelson HA, Schaefer SY, Beeman SC, Verpeut JL. Arizona State University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is the most common cause of dementia and is characterized by accumulating amyloid beta plaques and tau neurofibrillary tangles that lead to progressive neurodegeneration and cognitive decline. Emerging staging frameworks indicate that pathology is detectable >15 years prior to clinical symptom onset, such that individuals are cognitively asymptomatic while still at risk for dementia (Bateman et al., 2012). This highlights the need for tools that detect disease-related changes before cognitive decline, when interventions are most effective.

Plasma biomarkers have improved the ability to identify early pathology. However, these measures do not predict future cognitive and functional decline. In conjunction with these biomarker tests, objective fine-motor skill assessments have been developed that predict both decline and dementia progression in individuals with mild cognitive impairment (Schaefer et al., 2020). Evidence suggests that fine motor impairments emerge prior to gross motor deficits during preclinical stages, meaning such an assessment may serve as a more sensitive indicator of early disease-related change. The current study aims to further investigate fine motor decline using a transgenic AD rodent model, capturing progression from disease onset through advanced stages.

Methods: The TgF344-AD (Tg, n=12) rat was assessed in a novel fine-motor apparatus (Melick et al., 2025) from 6 to 24 months of age and compared with age-matched wildtype (Wt, n=12) controls. Cognition was evaluated in the Morris Water Maze, a test of spatial reference memory, with gross motor function tested using grip strength. Social LEAP Estimates Animal Poses (SLEAP) was used to examine fine motor behavior, including reach trajectory and task strategy.

Results: Tg rats exhibited impaired performance in the fine motor task across the lifespan, at 6 ($p < .001$), 12 ($p < .001$), 18 ($p = .0044$), and 24 ($p < .001$) months. In the MWM, Tg rats swam greater distances to the platform at 12 months ($p = .027$), indicating poorer performance that did not persist. Grip strength remained similar across ages. Tg rats showed significantly elevated plaque burden in hippocampal CA1 ($p = .0047$), motor cortex ($p < .001$), and cerebellar molecular layer ($p = .025$) compared to Wt at 10 months. Tg rats also had reduced pyramidal neuron dendritic complexity in the prelimbic cortex at 10 ($p = .002$) and 17 ($p < .001$) months.

Conclusions: Together, these findings suggest that functional fine motor decline may provide a more sensitive marker of AD-related dysfunction than conventional cognitive or gross motor measures, with the potential to detect disease-associated changes earlier in the progression of pathology.

STUDENT POSTER # 165

NEURONAL AGING REWIRES P-BODIES DYNAMICS. Miller B, Rhine K. University of Arizona; Arizona Alzheimer's Consortium.

Background: P-bodies are dynamic, molecular condensates that concentrate mRNA decay machinery and serve as key sites of post-transcriptional gene regulation. As long-lived post-mitotic cells, neurons cannot dilute damaged or dysregulated RNA through cell division, thereby placing greater demands on RNA quality-control mechanisms. Disruption in these mechanisms may contribute to the pathological aggregation of aberrant transcripts and proteins associated with neurodegenerative disease (NDD) such as Alzheimer's. Despite this, the composition, dynamics, and decay activity of P-bodies in aged neurons remain unknown.

Methods: To study neuronal aging, we used transdifferentiated neurons (tNs) derived from young and old human donors. tNs preserve the donor's transcriptomic and epigenetic age signatures, making them ideal for capturing aging-linked RNA regulatory changes in vitro. P-body number, size, and morphology were investigated in young and aged tNs by confocal microscopy using established P-body markers (EDC4, LSM4) and pathway-specific markers (XRN1, UPF1).

Results: Quantitative image analysis identified age-dependent changes in P-body morphology during neuronal aging, with P-bodies becoming smaller and more numerous in aged tNs. Metabolic RNA labeling with Click-It chemistry will be used to measure RNA kinetics and to identify whether functional changes accompany morphological changes in P-body biology.

Conclusions: Together, these findings will inform how P-body biology and RNA decay capacity are impacted by neuronal aging and their contribution to age-associated disruptions in RNA homeostasis.

STUDENT POSTER # 166

MULTIVARIATE ASSOCIATIONS BETWEEN COGNITION AND GAIT-BALANCE KINEMATICS IN OLDER ADULTS. Millmond E, Sutherland S, Ekstrom A, Hill P. University of Arizona; Arizona Alzheimer's Consortium.

Background: Declines in cognition and motor function are each common during healthy aging. Although often studied separately, growing evidence indicates that changes in motor function, such as gait and balance (i.e., functional mobility) correlate with cognitive factors and may reflect shared underlying neural mechanisms. Dual declines in cognition and gait have been shown to predict future dementia risk better than declines in either domain alone. However, prior work examining cognitive-gait associations has largely relied on single-domain pairings, such as correlations between gait speed and executive function. These types of approaches may miss meaningful latent multivariate associations between cognition and spatiotemporal gait features. To address this gap, this work aims to quantify shared covariance across cognition and sensor-based measures of gait and balance.

Methods: Seventy-six older adult participants (aged 64-89 years, mean age = 73 years) completed a standardized neuropsychological test battery that assessed multiple cognitive domains, including memory, visuospatial performance, executive function, and verbal abilities. Participants also completed standardized tests of gait, balance, and fall risk while wearable sensors recorded precise kinematic data with high spatiotemporal resolution. Raw scores from each of these measures were then z-scored and used to create composite measures of cognition and functional mobility. We used a partial least squares (PLS) analysis to identify patterns of shared covariance between the cognitive and functional mobility composites. This approach allowed us to identify latent variables that capture multivariate associations between the cognitive and functional mobility domains.

Results: The PLS analysis revealed a latent cognitive-gait variable that explained 68% of the cross-block covariance between the respective cognitive domains and spatiotemporal gait features. We computed bootstrap ratios (BSR) for the cognitive and functional mobility domain saliences to identify reliable contributors to the latent variable using a $|BSR| \geq 2$ cutoff. Contributing to this single latent variable were both cognitive and motor dependent measures. Cognitive contributions were from memory and visuospatial performance, with weaker and less reliable contributions from executive function and verbal abilities. For gait, this included a broader profile spanning multiple composite measures of gait speed, gait variability, and dynamic balance.

Conclusions: These findings suggest that cognitive-motor associations in older adults are not reducible to isolated pairings between a single cognitive measure and a single gait outcome. Instead, the strongest pattern emerged as a latent multivariate pattern linking memory and visuospatial performance with a broader gait profile spanning gait speed, gait variability, and dynamic balance. These findings support the value of multivariate approaches for capturing shared cognitive-motor variance that may be missed by traditional bivariate analyses.

STUDENT POSTER # 167

ACVR1C SIGNALING IN THE BASOLATERAL AMYGDALA REGULATES EXTINCTION OF TONE FEAR. Moon J, Rajput Y, Judd JM, Keiser AA. Arizona State University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive cognitive decline and early dysfunction of limbic regions including the amygdala. The amygdala, located in the medial temporal lobe, plays a central role in processing emotional salience, particularly fear and anxiety, and is critical for the formation and regulation of fear-related memories. Early in AD, structural and functional alterations of the amygdala, including atrophy, are associated with impairments in emotional learning and memory. Within the amygdala, the Basolateral Amygdala (BLA) is a key node for fear conditioning, supporting the acquisition, consolidation, and extinction of fear memories. In particular, extinction learning, which is the process by which learned fear responses are reduced through repeated non-reinforced exposure, is a dynamic form of memory updating that is essential for adaptive emotional regulation. This process is regulated by GABAergic inhibitory synaptic transmission within the BLA which is impaired in neurodegenerative diseases like AD, yet the signaling pathways underlying these effects is not completely understood. We recently identified Activin A Receptor Type 1C (ACVR1C), a TGF-β type I receptor, as a bidirectional regulator of hippocampal-dependent memory. Disruption of Acvr1c in dorsal hippocampus through expression of an AAV1 kinase-dead mutant construct impaired performance in both object location memory (OLM) and contextual fear conditioning (CFC) while the overexpression of wild-type Acvr1c (WT) enhanced performance in OLM. Given the role of ACVR1C in regulating memory strength in hippocampal circuits, we now extended this work to investigate its role in the basolateral amygdala. Specifically, we tested whether Acvr1c modulates BLA-dependent extinction of tone fear, a process critical for adaptive fear regulation and potentially disrupted in neurodegenerative disease.

Methods: To determine whether ACVR1C signaling in the Basolateral Amygdala (BLA) regulates BLA-dependent fear extinction, we injected 8-week-old male and female C57BL/6J mice with kinase-dead Acvr1c (KD) AAV1 construct or empty vector (EV) via bilateral stereotactic injections into BLA at AP: minus 1.4mm, ML: plus-minus 3.1 mm, DV: minus 4.9 mm coordinates. After three weeks to allow for viral expression, mice underwent cued fear conditioning, followed by context and cue memory testing and extinction training. Anxiety-like behavior was assessed using elevated plus maze and open field. Motor coordination was tested with the beam balance.

Results: The Acvr1c KD mice maintained higher freezing to tone late in extinction compared with their EV counterparts which suggests more robust fear memory in the KD mice. In elevated plus maze, the Acvr1c KD mice spent less time in the open arms compared with their EV counterparts, indicating a higher level of anxiety-like behavior.

Conclusions: Together, these data implicate ACVR1C as a key mediator of extinction and anxiety-like behavior in BLA. Ongoing analysis on the tissue will provide deeper insight into the mechanisms by which ACVR1C regulates the extinction of tone fear.

STUDENT POSTER # 168

SUBCLINICAL EPILEPTIFORM ACTIVITY IN ALZHEIMER'S DISEASE-SPECTRUM COGNITIVE IMPAIRMENT: A SCOPING REVIEW OF DETECTION METHODS, SLEEP-STATE DEPENDENCE, AND CLINICAL RELEVANCE. Moxam C, Green J, Sundman M, Chou Y. University of Arizona; Arizona Alzheimer's Consortium.

Background: Subclinical epileptiform activity (SEA) may be underrecognized in Alzheimer's disease and related cognitive-impairment states. However, reported prevalence and clinical relevance vary widely, suggesting that SEA detection may depend strongly on recording and scoring methods.

Methods: We conducted a PRISMA-ScR scoping review within a prospectively registered OSF protocol. Searches of PubMed/MEDLINE, Embase, PsycINFO, Scopus, and Web of Science identified 5,168 records; 1,762 duplicates were removed. Following title/abstract and full-text screening, the parent evidence map was narrowed before final synthesis to support focused analyses. This manuscript synthesizes records charted as direct SEA/epileptiform-activity evidence and detection-methods evidence. Two reviewers independently charted eligible sources using a structured workbook. Results were synthesized descriptively; no meta-analysis or formal risk-of-bias assessment was performed.

Results: The SEA-focused synthesis included 32 unique article-level records: 29 direct epileptiform-activity records and 17 detection-methods records, with 14 records contributing to both categories. Detection varied by recording duration, sleep capture, montage, source sensitivity, event definition, and scoring threshold. Brief routine EEG identified SEA in a minority of Alzheimer's disease patients, whereas prolonged, sleep-inclusive, multimodal, high-density, ear-EEG, MEG, and foramen ovale approaches often detected additional activity. Several studies associated SEA with cognitive decline, neuropsychiatric symptoms, seizure risk, or antiseizure-treatment response.

Conclusions: SEA is a clinically relevant but method-dependent feature of Alzheimer's disease-spectrum cognitive impairment. Future studies should use standardized event definitions, prolonged sleep-inclusive monitoring, burden-based metrics, and biomarker-characterized longitudinal cohorts.

STUDENT POSTER # 169

CHRONIC GLIAL ACTIVIATION IN ALZHEIMER'S DISEASE DRIVES A TUMOR-SUPPRESSIVE IMMUNE LANDSCAPE. Nascari DG, Beniwal AS, Bouchal SM, Rabichow BE, Eghlimi R, Dufault M, Gibson KA, Grief D, Flick MJ, Alton BD, Parrish FM, Tran I, Williams-Katek AL, Mee ED, Banovich NE, Donev K, Blomquist MR, Fortin Ensign SP, Tran NL, Fryer JD. Mayo Clinic Arizona; Translational Genomics Research Institute; University of California, San Francisco; Arizona Alzheimer's Consortium.

Background: Glioblastoma (GBM) and Alzheimer's disease (AD) are two age-related disorders with poor clinical outcomes and limited effective therapies. Population-based studies have consistently reported an inverse association between AD and several malignancies, including GBM, with individuals affected by AD demonstrating a substantially lower incidence of cancer. In previous studies using APP^NL-G-F^/MAPT double knock-in mice, we found that established AD pathology limited glioma progression through reduced tumor engraftment and invasion, prolonged survival, and increased recruitment of immune cells into the tumor microenvironment. We proposed that chronic neuroinflammation associated with AD establishes an immune landscape that is unfavorable for GBM growth.

Methods: Age-matched APP^{NL-G-F}/MAPT double knock-in (AD) and wild-type (WT) mice underwent orthotopic implantation of syngeneic GL261 or SB28 glioblastoma cells. Immune populations within tumor-bearing brain tissue, cervical draining lymph nodes, and spleens were characterized by flow cytometry using complementary myeloid and lymphoid panels. To determine whether these observations extended to patients, tumor specimens from 28 individuals with GBM were retrospectively analyzed and divided into two equal cohorts based on the presence or absence of incidental amyloid-β deposition in the surrounding brain parenchyma identified by histopathology.

Results: Consistent with our earlier observations, AD mice demonstrated improved survival and diminished tumor progression relative to WT controls. Immune profiling revealed a coordinated activation of innate and adaptive immunity, characterized by increased activation of myeloid populations together with enhanced T-cell activation and effector function in the brain, draining lymph nodes, and spleen. Analysis of the human validation cohort produced similar findings. GBM specimens from patients with adjacent amyloid-β deposition exhibited greater myeloid activation, measured by LGALS expression, and approximately threefold greater infiltration of effector T cells compared with tumors lacking amyloid pathology.

Conclusions: The concordance between the murine and human datasets provides biological support for the reported inverse relationship between Alzheimer's disease and glioblastoma. These findings suggest that AD-associated neuroinflammation promotes a systemic and local anti-tumor immune response capable of restricting GBM progression. Therapeutic strategies that selectively harness neuroinflammatory immune pathways may represent a promising direction for future glioblastoma immunotherapy.

STUDENT POSTER # 170

GENERATION OF ISOGENIC APOE3[R145C]/4 HIPSC LINE TO MODEL ALZHEIMER'S DISEASE RISK IN AFRICAN ANCESTRY. Nguyen M, Billingsley K, Brafman D. Arizona State University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD), the most common cause of dementia, was officially listed as the sixth-leading cause of death in the United States, with an estimated 6.9 million Americans age 65 and older living with Alzheimer's dementia today. Variants of the APOE gene have been identified as the most significant genetic risk factor for late-onset AD. Particularly in people of African ancestry, the APOE R145C missense variant (rs769455) increases AD risk nearly threefold in E3[R145C]/E4 carriers compared to canonical E3/E4 individuals. Despite this strong epidemiologic association, the biological mechanisms by which APOE R145C alters disease-relevant pathways remain undefined. In this study, the generation of isogenic Human Induced Pluripotent Stem Cells (hiPSCs) will provide a versatile system for mechanistic studies of this variant.

Methods: To enable precise single-nucleotide editing at the endogenous APOE locus, we designed the single-guide RNAs (sgRNAs) that are compatible with PAM-flexible CRISPR-based cytosine base editor xCas9(3.7)-BE4. This allows the expansion of targetable genomic space, thereby being able to introduce the single nucleotide substitution responsible for the R145C amino acid change, converting Arginine [CGT] to a Cysteine [TGT]. The molecularly cloned sgRNAs with hiPSC-optimized pEF1a promoter PAM-flexible editor were delivered into hiPSCs using lipid nanoparticles and combined with fluorescence-based transient reporter system, which enriches the editing efficiency. We used fluorescence microscopy to confirm the editing activity and performed single-cell sorting to derive clonal edited lines. Edited hiPSC lines will be characterized for pluripotency, genomic stability, and differentiation capacity.

Results: APOE-targeting sgRNAs were designed to position the target cytosine at the optimal editing window and cloned into the pDT-sgRNA backbone for subsequent BIG-TREE transient reporter system base editing experiments. We successfully validated the pCMV-xCas9(3.7)-BE4 PAM-flexible editor by first transfecting it into HEK293 cells and then hiPSCs to generate APOE3[R145C]/4 line. Cells that expressed GFP+ were single and bulk sorted using a Fluorescence-Activated Cell Sorting (FACS) machine for clonal expansion and efficiency assessment.

Conclusions: Sorted hiPSCs carrying the R145C variant are undergoing clonal expansion. This hiPSC model will be utilized to differentiate into neurons, astrocytes, and brain organoids to further study the genotype-to-phenotype relationships in AD. Particularly, they can help identify how the APOE R145C variant alters lipid metabolism, neuroinflammation, and amyloid/tau pathology, enabling the development of more precise therapeutic strategies and improving genetic risk prediction for underrepresented populations. Ultimately, this work may contribute to reducing disparities in AD diagnosis, treatment, and clinical outcomes in African ancestry populations.

STUDENT POSTER # 171

DYNAMIC CHANGES IN TAU POST-TRANSLATIONAL MODIFICATIONS DURING HEALTHY AND NEURODEGENERATIVE AGING REVEAL EARLY TAU ALTERATIONS. Nordbeck AJ, Tseng J-H. Arizona State University; Arizona Alzheimer's Consortium.

Background: Tau is an intrinsically disordered microtubule-associated protein that appears in six different isoforms within neurons. These isoforms perform diverse roles in neuronal physiology, including regulation of microtubule stability and intracellular transport. These functions are dynamically regulated by an extensive array of post-translational modifications (PTMs) that collectively shape tau conformation, interactions, localization, and turnover, with effects that may be beneficial or detrimental. It is believed that aberrant tau PTMs lead to unbinding, mislocalization, and aggregation of toxic tau neurofibrillary tangles (NFTs) in diseases known as tauopathies. Abnormal PTMs are thought to drive disease pathology and progression, as tau PTMs vary throughout the stages of Alzheimer's Disease (AD). Research has shown that different combinations of PTMs regulate tau conformation and activity, thereby altering tau function and toxicity. However, to our knowledge, there have been no studies investigating longitudinal differences between the healthy or diseased aging of tau.

Methods: This project will collect brain tissue from WT mice at 5 ages between 1 and 12 months and assess the progressive changes in tau PTMs throughout healthy and diseased aging. The brain tissue will be homogenized and separated into soluble and insoluble fractions. Fractions will be used for Western Blotting to assess protein abundance, modifications, and changes to functional pathways. Further purification and isolation of tau will be performed using immunoprecipitation with a total tau antibody. Purified tau samples will then be subjected to high-resolution mass spectrometry to comprehensively characterize post-translational modifications, including modification type, site occupancy, and relative abundance. The data collected will be further analyzed to identify age-dependent PTM patterns. Similarly, disease models, such as PS19 mice, and pathological human tissue will be assessed under similar methodological conditions and compared to the healthy aging datasets. Additional model systems, such as HEK 293 and primary cortical mouse neurons, will be used in conjunction to assess healthy and diseased tau modifications.

Results: We identified fourteen phosphorylation sites, including several associated with tau pathology and clinically relevant tau biomarkers. Interestingly, phosphorylation at the AT8 epitope and several additional disease-associated sites showed transient alterations during midlife before declining at later ages, suggesting that early aging-related tau changes may differ from classical late-stage tau pathology. In contrast, several phospho-tau biomarker sites displayed progressive age-dependent increases.

Conclusions: Together, these findings support the concept that tau PTMs develop dynamically during normal aging and may represent early molecular events that increase vulnerability to neurodegeneration. Ongoing studies are extending these observations to human brain tissue and evaluating whether targeting tau regulatory pathways can modify age-associated tau alterations in vivo.

STUDENT POSTER # 172

INDIVIDUALIZED ELECTRIC FIELD STRENGTH AND MEMORY OUTCOMES FOLLOWING TMS IN MILD COGNITIVE IMPAIRMENT. Norman SL, Liu Y, Green JM, Haaheim LG, Siu HM, Dannhauer M, Chou YH. University of Arizona; East Carolina University; Arizona Alzheimer's Consortium.

Background: Mild cognitive impairment (MCI) increases risk for Alzheimer's disease and is associated with early deficits in associative memory, a key target for intervention. Transcranial magnetic stimulation (TMS) may support cognition in MCI, but treatment response varies considerably across individuals, and conventional motor threshold based dosing may not capture stimulation actually delivered to non-motor targets. This study examined whether individualized electric field (E-field) modeling predicts associative memory outcomes following TMS to the left posterior parietal cortex in MCI, and compared E-field modeling against three motor threshold-based calibration approaches, including the APEX adjusted method, which scales motor threshold by an E-field derived efficiency ratio between motor cortex and the stimulation target.

Methods: Sixty older adults with MCI (ages 52 to 79) completed a three-condition randomized crossover trial of intermittent theta burst stimulation (iTBS), continuous theta burst stimulation (cTBS), and sham stimulation, delivered to an individualized left posterior parietal target at 70% of resting motor threshold (RMT). Associative memory was assessed before and after each block using the Face Name Associative Memory Exam (FNAME), with d prime and accuracy (active minus sham) as outcomes. Structural MRI was used to construct individualized finite element models in SimNIBS, from which E-field magnitude and the E-field normal component were extracted at the stimulation target. Three motor threshold-based calibration approaches were also derived for comparison: standard RMT, distance adjusted motor threshold (incorporating coil to cortex distance), and an APEX adjusted motor threshold, which scales motor threshold by the ratio of E-field efficiency at the target relative to the motor cortex. Linear mixed effects models (covariates: age, education, sex, parietal volume, cortical thickness) tested associations between each calibration metric and memory outcomes, with model fit compared using Akaike Information Criterion (AIC).

Results: Individualized E field magnitude significantly predicted d prime (standardized β 0.34, $p = .002$) and accuracy ($p = .017$), and this relationship did not differ significantly between iTBS and cTBS (interaction $p = .325$), indicating a relationship consistent across stimulation protocols. In contrast, neither standard RMT ($p = .259$) nor distance adjusted motor threshold ($p = .247$) significantly predicted d prime. The APEX adjusted motor threshold, however, did significantly predict d prime ($p = .006$, standardized β of -0.33), and outperformed standard RMT and distance adjusted motor threshold in direct model comparison among participants with complete data across all calibration methods (ΔAIC of 0.0 for APEX versus 8.9 and 9.4, respectively).

Conclusions: Individualized E field modeling captures a clinically meaningful dose response relationship between stimulation and associative memory in MCI that conventional motor threshold-based calibration fails to detect. Incorporating an APEX adjustment, which accounts for the efficiency of field transmission from the motor cortex to the stimulation target, meaningfully improves on standard motor threshold approaches, though it does not yet match the predictive value of direct E field modeling. Together, these findings support a shift toward computationally guided, individualized dosing to improve the precision and consistency of TMS based interventions in MCI.

STUDENT POSTER # 173

REMOVED BUT NOT FORGOTTEN: INVESTIGATING THE AGE-DEPENDENT COGNITIVE EFFECTS OF HYSTERECTOMY IN A FEMALE RAT MODEL. Oevermann M, Corbin S, Doyle R, Pastor J, Lizik CR, Wu E, Bimonte-Nelson H. Arizona State University; Arizona Alzheimer's Consortium.

Background: Hysterectomy, the surgical removal of the uterus, is the most common gynecologic procedure in the United States, with 22% of U.S. women over the age of 45 undergoing the procedure. Despite non-invasive alternatives for some benign indications, hysterectomy procedures persist and can occur during any stage of a woman's life, spanning young adulthood to postmenopause. Some research has shown that hysterectomy with ovarian retention increases the risk for dementia, a finding that is exacerbated when the surgery occurs at younger ages, implicating surgery age as a variable of interest. We have shown analogous findings in preclinical models, with impairments to spatial working memory in young hysterectomized rats extending to one year after surgery. Currently, no preclinical work has explicitly evaluated age at hysterectomy surgery as a variable of interest, with a focus of surgery occurring in late adulthood. The present study aimed to systematically address this research gap by administering hysterectomy to two age groups spanning young to aged timeframes, thereby directly assessing whether the cognitive impacts of hysterectomy differ by age at initiation.

Methods: Young and aged female rats from the NIA colony were randomly assigned to receive either Sham-control surgery or Hysterectomy (Hyst). Vaginal smears were assessed to confirm estrous cyclicity in all rats following surgical procedures. A behavioral battery was implemented and included the water radial-arm maze (WRAM), the Morris water maze (MWM), and the delayed-match-to-sample (DMS) plus maze to examine impacts to spatial short-term, working, and reference memory. Finally, all rats were tested on the visible platform (VP) control task to assess for competencies of visual, ambulatory, and water-maze procedural components.

Results: Aging resulted in poorer cognitive performance in both Sham and Hyst groups, with aged rats making more errors compared to young rats for each surgery type, for each behavior tasks. Hysterectomy yielded unique deficits to both spatial working and reference memory. All rats successfully completed the VP task indicating competence of procedural water-maze performance, and the expected cyclicity status was noted for all surgery groups for vaginal smear assessments with no differences between uterus-intact sham and hysterectomy rats within each respective age cohort.

Conclusions: The current results demonstrate broad age-related decreases in performance across multiple memory domains, and that detrimental effects of hysterectomy occur when surgery is initiated during young or aged timeframes. Moreover, effects were not due to issues in motoric, visual, or procedural components. The present study replicates and extends our prior findings of hysterectomy, underscoring that detriments resulting from uterine removal with ovarian conservation persist across multiple ages and timeframes following surgery. This research adds to the growing scientific landscape actively overturning prior dogma by asserting that the non-pregnant uterus is indeed involved in factors that reach beyond reproduction, including but not limited to cognition.

STUDENT POSTER # 174

ASSESSING THE EFFECTS OF NRF2 AND E2/P4 LOSS QUIESCENCE-ACTIVATION-SENESCENCE BALANCE OF STEM CELLS IN THE AGING RODENT BRAIN. Pillutla SVP, Corenblum MJ, Mutha A, Anderson D, Yamamoto M, Madhavan L. University of Arizona; Tohuku University; Arizona Alzheimer's Consortium.

Background: Dynamic adult neural stem and progenitor cells (NSPCs) in the subventricular zone (SVZ) and subgranular zone (SGZ) transition between quiescence, activation and senescence (Q-S-A) subject to the influence of extrinsic and intrinsic factors. Our prior work established a midlife window of reduced neurogenesis at 13-15 months (m) in male Fisher (F)344 rats mediated by reduced transcription factor, Nrf2, expression. In females, while age-related neurogenic decline occurred at 14m, an additional vulnerable time was observed when ovariectomy (OVX)-induced loss of estradiol (E2) and Progesterone (P4) accelerated this decline to 9m. Further, neurogenic function was rescued with overexpression of Nrf2 before 13m in males or E2/P4 replacement in OVX females before 9m establishing their causative role. Our running hypothesis is that age, Nrf2, and E2/P4 affect the crucial balance between NSPC Q-S-A enhancing senescence to drive the emergence of the vulnerable midlife time-windows in the male and female brains.

Methods: To test this, we used Nrf2 knock out (Nrf2-KO) and wild-type (WT) F344 rats aged 14-15m in males and 10-11m in females relevant to their midlife time-windows, comparing them to younger rats. In females, sham and OVX surgeries were performed to probe the impact of E2/P4 loss. Animals were subjected to NSPC-specific behavioral tests, fine olfactory discrimination (FOD, relays SVZ NSPC function) and object-context pattern separation (OCPS, relays DG NSPC function). Immunohistochemical (IHC) and immunoblotting assays are used to assess NSPC Q-S-A balance.

Results: Nrf2-KO rats performed poorly at both FOD and OCPS tasks after their respective vulnerable time-windows at 14-15m in males & 10-11m in females. This effect was further exaggerated with OVX in Nrf2-KO females. IHC data thus far indicate an increase in the number of senescent NSPCs (sNSPCs) in SVZ with age and Nrf2-KO while quiescent and activated NSPCs reduced in males. In females, sNSPCs increased with age (10-11m), and individually with OVX and Nrf2-KO at the younger age (6-7m).

Conclusions: Broadly, our work will help understand the changes in Q-S-A balance underlying the dramatic reduction in adult neurogenesis during midlife and support the identification of targets for future therapeutics for aging and neurodegeneration precisely applicable to males and females

STUDENT POSTER # 175

CENTRAL RETINAL VENULAR EQUIVALENT DISCRIMINATES ALZHEIMER'S DISEASE IN UK BIOBANK. Pitea R, Wang V, Li X, Langlais B, Dumitrascu O. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Retinal vascular measures provide a direct and objective modality to study Alzheimer's disease (AD) associated vasculopathy. Herein, we aimed to study the correlation between automatically quantified retinal arteries and veins diameters and AD in UK Biobank.

Methods: We identified 1,039 UK Biobank participants with good-quality macula-centered color fundus photographs (220 AD, 202 Parkinson's disease [PD], 516 normal controls [NC]). Retinal eye central vein equivalent (CRVE), artery equivalent (CRAE), and arterio-venous ratio (AVR) were quantified in Hubbard zones B and C using Automorph. Regression models compared adjusted means and mean differences for AD vs NC and AD vs PD, controlling for age, gender, hypertension, diabetes (DM), and APOE4 carriage.

Results: AD subjects were older than NC (64.9 ± 4.4 vs 55.9 ± 8.1 years, $p<0.001$) and PD (64.9 ± 4.4 vs 62.6 ± 5.3 years, $p<0.001$), and more frequently APOE4 carriers (vs NC 64.4% vs 30.8%, $p<0.001$; vs PD 64.4% vs 29.6%, $p<0.001$). Rates of hypertension and DM were similar between groups except for higher DM in AD vs NC ($p=0.04$). CRAE, CRVE, and AVR showed strong inter-eye correlation. Between AD and NC, age and DM adjusted retinal vascular measures showed greater CRVE in Hubbard zone B (mean difference (CI) 2.042 (0.61, 3.47), $p=0.005$) and zone C (mean difference (CI) 1.859 (0.41, 3.29), $p =0.01$). After additional adjustment for APOE4, CRVE in zone B only remained significantly greater in AD when compared to NC (mean difference (CI) 1.97 (0.15, 3.79), $p=0.03$). When we compared AD and PD subjects, age and gender adjusted retinal vascular measures also exhibited greater CRVE in AD in both zones B and C, that remained significant after additional adjustment for APOE carrier status (mean difference (CI) 2.531 (0.946, 4.117), $p=0.0018$). CRAE and AVR showed non-significant differences between AD and NC, as well as AD and PD, in all zones ($p>0.05$ for all comparisons).

Conclusions: The central retinal vein equivalent was significantly greater in subjects with AD in the UK Biobank, after adjusting for demographic, vascular co-morbidities and APOE4 carrier status. These results suggest that wider retinal venules are indicators of AD-associated retinal vasculopathy and degeneration.

STUDENT POSTER # 176

AGING IN CONTEXT: ENHANCED EPISODIC SPECIFICITY AND SOCIOEMOTIONAL CONTENT IN OLDER ADULTS' EVERYDAY AUTOBIOGRAPHICAL THOUGHTS – INSIGHTS FROM THE MIND WINDOW APP. Puig Rivera VA, Cervantes LJ, Andrews ES, Freveletti D, Grilli MD, Andrews-Hanna JR. University of Arizona; Northeastern University; Arizona Alzheimer's Consortium.

Background: Cognitive aging research has long suggested that older adults' autobiographical memories and future thoughts lack episodic detail and spatiotemporal specificity compared to younger adults, often resulting in general or "semanticized" recollections. These findings, alongside age-related neural changes, have contributed to a dominant, decline-oriented view of aging and autobiographical thought. However, a growing body of work suggests that such age effects may partly reflect the social and contextual constraints of laboratory-based settings, which lack the personal environmental cues older adults rely on in daily life. This work examines this by sampling real-time autobiographical thoughts as they naturally arise, expanding our current understanding of cognitive aging.

Methods: Across two studies, we examined autobiographical thinking in real-world settings using ecological momentary assessment (EMA). In Study 1, a large adult lifespan sample (N = 3,847; ages 18-89) used Mind Window, a freely available smartphone app developed by our research group, to report on autobiographical thoughts in daily life via six random daily prompts assessing mood and thoughts preceding the app notification. We focused on five dimensions: episodic specificity, vividness, affective content, self-focus, and social orientation. Free-response descriptions were analyzed using linguistic tools to assess concreteness, perceptual detail, emotional tone, and social referencing. Linear mixed-effects models examined age group as the primary predictor of each dimension. Age was additionally modeled as a linear and quadratic predictor to capture continuous lifespan trajectories. Study 2 (preregistered on OSF) replicated this approach in 75 young adults (18-34) and 142 older adults (60-84), who also completed the Autobiographical Interview, a validated lab measure of episodic memory specificity, enabling within-person comparison across contexts.

Results: Contrary to typical lab-based findings, older adults in both studies reported significantly greater episodic specificity, vividness, and positive affective content in daily life, along with a shift from self-focused to more socially oriented thinking. Linguistic analyses corroborated these patterns: older adults' descriptions were more concrete, with more perceptual words, positive tone, third-person pronouns, and social referencing, and less first-person language. In Study 2, the same older adults showed the expected reduction in episodic detail on the lab-based Autobiographical Interview, consistent with prior literature. Study 1 models also revealed gradual, non-linear change: episodic specificity and vividness rose steadily from young to middle to older adulthood, while affective content increased steeply after midlife. Episodic specificity, affective content, self-focus, and social focus all showed significant non-linear trajectories, while vividness increased linearly with age.

Conclusions: These findings challenge the assumption that aging entails a universal loss of episodic detail, suggesting instead that lab-based declines may reflect contextual factors such as narrative goals, stereotype threat, or the absence of familiar retrieval cues. The observed increases in positive, socially oriented content align with theories of socioemotional selectivity and the age-related positivity effect, suggesting that affective and motivational factors actively support episodic richness in older age. Future work will examine the mechanisms underlying these patterns and how they interact with retrieval context. Together, this work highlights the role of motivational and contextual factors in autobiographical thought across the lifespan and underscores the unique value of EMA for ecologically grounded theories of cognitive aging.

STUDENT POSTER # 177

NEURONAL AGING ALTERS STRESS GRANULE MORPHOLOGY AND DYNAMICS IN RESPONSE TO ENVIRONMENTAL AND CELLULAR STRESS. Pulliam S. University of Arizona; Arizona Alzheimer's Consortium.

Background: Environmental and cellular stressors accumulate with neuronal aging, increasing susceptibility to neurodegenerative diseases (NDDs). Stress granules (SGs) are dynamic molecular condensates that transiently sequester non-translating mRNAs and RNA-binding proteins in response to stress. While SGs are typically dynamic, prolonged stress can promote a transition to gel- or solid-like states associated with the formation of pathological protein aggregates observed in disorders such as Alzheimer's disease. However, the extent to which neuronal aging influences SG morphology, dynamics, and composition in response to environmental stressors remains unknown.

Methods: To investigate this question, we used transdifferentiated neurons (tNs) generated by direct conversion of patient-derived fibroblasts into neurons that retain age-associated cellular features. Young and aged tNs were exposed to various stressors modeling proteasomal inhibition, oxidative, endoplasmic reticular, osmotic, and thermal stresses.

Results: These stressors altered SG morphology differently in aged tNs relative to young tNs. Live-cell imaging and fluorescence recovery after photobleaching (FRAP), paired with mass spectrometry of core SG immunoprecipitants, will further characterize these changes in SG morphology.

Conclusions: Together, these studies help define how aging alters neuronal stress responses and how environmental stressors contribute

STUDENT POSTER # 178

PLASMA PROTEOMIC SIGNATURES OF ALZHEIMER'S DISEASE RISK ARE DIFFERENTIALLY SHAPED BY MENOPAUSAL HORMONE THERAPY FORMULATION, INITIATION TIMING, AND APOE GENOTYPE IN POSTMENOPAUSAL WOMEN. Ragsdale SM, Holmgren G, Vitali F, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) disproportionately affects women, with nearly two-thirds of cases occurring in females and incidence accelerating after menopause. The APOE4 allele is the strongest genetic risk factor for late-onset AD, conferring 3–12-fold increased risk and is associated with reprogrammed metabolic and inflammatory networks in postmenopausal women. While the menopausal transition can be a critical neurobiological vulnerability window, the impact of menopausal hormone therapy (MHT) timing and formulation on AD risk remains unresolved. We investigated the impact of how MHT timing, "early" (5 years), and formulation (estrogen-only vs combined estrogen + progestogen) may differentially modulate AD-relevant biology depending on APOE genotype. Resolving this three-way interaction is essential for precision AD prevention.

Methods: Using UK Biobank plasma proteomic data from a curated cohort of 4,590 postmenopausal women, we examined protein level differences stratified by MHT formulation, initiation timing, and APOE genotype (APOE2 carriers, E3/E3 homozygotes, APOE4 carriers). Differential protein expression analysis was performed across multiple comparisons including MHT use, MHT use in APOE4 carriers, and MHT use in AD patients. Pathway enrichment and network analyses were conducted using Ingenuity Pathway Analysis (IPA), STRING protein-protein interaction networks, Gene Ontology Biological Processes (GO:BP), Gene Set Enrichment Analysis (GSEA), KEGG pathway mapping, Reactome pathway database, and Over-Representation Analysis (ORA) to provide comprehensive functional characterization of differentially expressed proteins. Principal component analysis was performed to characterize the distribution of proteomic variation across groups.

Results: Early initiators began MHT 2.5–2.8 years post-menopause versus 10.8–13.2 years for late initiators. APOE4 carriers demonstrated approximately 7-fold higher AD incidence compared to E3/E3 homozygotes ($p<0.001$), consistent with established genetic risk effects. Differential expression analysis revealed 167 proteins between MHT users and non-users, and 185 differentially expressed proteins (DEPs) in MHT users versus non-users among APOE4 carriers. IPA analysis across all comparisons identified 657 significantly enriched pathways ($p<0.05$) spanning immune/inflammatory (n=51), cell signaling/survival (n=29), metabolic (n=15), vascular/cardiovascular (n=15), brain/neurotransmitter (n=12), estrogen/hormone (n=12), Alzheimer's/neurodegeneration (n=10), ECM/tissue remodeling (n=10), lipid/fatty acid metabolism (n=10), and mitochondrial/mTOR (n=5) categories.

Conclusion: These findings suggest that MHT formulation and timing produce differential proteomic signatures that vary by APOE genotype, indicating that hormone therapy may engage genotype-dependent molecular programs rather than uniformly protecting against or exacerbating AD-related biology. This work identifies candidate biological modifiers of postmenopausal AD risk and provides a basis for developing appropriately timed, genotype-informed hormone therapy strategies, addressing the critical need for sex-specific AD prevention.

STUDENT POSTER # 179

POSE ESTIMATION AS A BEHAVIORAL SCREENING TOOL FOR FUNCTIONAL GENETIC MODIFIERS OF NEURODEGENERATION. Rausch M, Bhattacharya M. University of Arizona; Arizona Alzheimer's Consortium.

Background: Although transcriptomic and multi-omic studies have identified hundreds of expression changes associated with neurodegeneration, the functional consequences of these changes on motor behavior remain largely unknown. Determining whether these alterations are drivers, compensatory responses, consequences, or bystanders in disease progression remains a critical challenge. To address this gap, we developed a behavioral screening platform using non-invasive pose estimation to quantify early motor dysfunction in Drosophila models of neurodegeneration.

Methods: Causal human ALS genes, including C9orf72 dipeptide repeats(Poly-GR36, Poly-PR36) and SOD1, were expressed in adult fly motor neurons. Flies were evaluated longitudinally on Days 1, 7, 14, and 21, with extended analysis to Day 28 when possible. Walking behavior was recorded and analyzed using SLEAP-based pose estimation and custom Python pipelines to quantify locomotor velocity and inter-limb cross-correlation as measures of motor output and coordination.

Results: Poly-GR36-expressing flies exhibited the earliest and most pronounced motor impairments among the genotypes examined. Coordination deficits were detectable as early as Day 1 and preceded measurable declines in locomotor velocity. Compared with mCherry controls and the other ALS models tested, poly-GR36 flies displayed the greatest reductions in coordination, followed by progressive impairments in velocity. Across all genotypes, coordination metrics were more sensitive than velocity for detecting early motor dysfunction.

Conclusions: Pose estimation provides a rapid, scalable, and non-invasive platform for functional screening of candidate genes identified through transcriptomic and multi-omic studies. Ongoing work applies this framework to evaluate the effects of a candidate modifier pathway, Toll signaling, on the poly-GR36 model. Together, these findings establish quantitative behavioral tracking as a sensitive platform for early phenotyping and genetic modifier screening in models of neurodegeneration.

STUDENT POSTER # 180

IDENTIFYING NEUROPSYCHOLOGICAL CORRELATES OF A BRIEF PERFORMANCE-BASED TEST OF COGNITION AND DAILY FUNCTIONING IN COGNITIVELY UNIMPAIRED OLDER ADULTS: FINDINGS FROM THE APOE 2.0 COHORT. Reed AM, Tomlin KB, Malek-Ahmadi M, Liang WS, Woodruff B, Langbaum JB, Reiman EM, Schaefer SY. Arizona State University; Banner Alzheimer's Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Performance-based tests of cognition and daily functioning may be more objective and less biased than clinician-rated measures for early screening of dementia risk; however, existing performance-based tests are often too long and burdensome for practical clinical use. We have therefore developed and validated a brief performance-based test for early dementia screening that involves four repeated timed trials of a functional fine motor task, which yields an intraindividual variability score where higher scores reflect poorer cognitive ability. While prior work in cognitively impaired older adults across the Alzheimer's disease (AD) spectrum has shown that the performance-based test primarily involves visuospatial and executive function, it is unknown whether similar cognitive domains are involved in asymptomatic individuals as well. Thus, the purpose of this study was to characterize the association between neuropsychological test scores and performance-based test scores in cognitively unimpaired older adults. We hypothesized that assessments of visuospatial and executive function would have the strongest associations with the performance-based test.

Methods: Data from 313 cognitively unimpaired individuals (mean +/- SD age 67.46 +/- 9.10 yrs; 68% female) were collected through the Banner Alzheimer's Institute APOE 2.0 cohort. All participants had a global Clinical Dementia Rating of 0 at the time of evaluation. The performance-based test included four consecutive timed trials of functional upper extremity movement (i.e., using the nondominant hand to transport beans with a spoon to target cups in a repeating sequence), yielding a standard deviation score for each participant with higher values indicating more (worse) intraindividual variability. Unsupervised classification and regression tree analysis (with a minimum terminal node = 31) was then used to empirically identify which neuropsychological tests from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set version 4 (UDSv4) predicted trial time variability.

Results: Across participants, mean +/- SD trial time variability on the performance-based test was 7.600 +/- 4.44 seconds. Regression tree analysis indicated that trial time variability was most strongly associated with tests of episodic memory, visual memory, and verbal memory (RMSE = 2.77 – 5.52, R-squared = 0.11).

Conclusions: These findings highlight the cognitive processes that may underlie our brief and objective performance-based test. These findings also suggest that there are subtle cognitive differences relevant to AD in cognitively unimpaired older adults and support future use of the performance-based test as a potential clinical measure to screen for preclinical Alzheimer's disease quickly and objectively when compared to other common screening measures.

STUDENT POSTER # 181

INTER-EYE DIFFERENCE IN RETINAL VASCULAR TORTUOSITY PREDICTS VERBAL MEMORY. Rich C, Dumitrascu O, Dumkrieger G, Woodruff B, Baxter L, Wang Y, Zheng K. Mayo Clinic Arizona; Arizona State University; Arizona Alzheimer's Consortium.

Background: The retinal microvasculature mirrors cerebrovascular health and correlates with cognitive performance. Although retinal imaging offers a non-invasive assessment of cerebral structure and function, thus far inter-ocular differences and fair right-left eye correlations have been reported in prior studies. Herein, we evaluated the correlations between cognitive performance with single-eye and absolute inter-eye differences in retinal microvascular measures in a cohort of cognitively intact individuals.

Methods: Bilateral macula-centered color fundus photographs from 280 cognitively intact participants were analyzed using Automorph. After quality control, 121 left-eye and 138 right-eye images were retained. Six microvascular features (vessel density, tortuosity density, squared curvature tortuosity, distance tortuosity, fractal dimension, and vessel caliber) were automatically quantified across the entire region, zone B and zone C, for arteries, veins and all vessels. We derived interocular asymmetry as the absolute inter-eye difference (diff[abs] = |left − right|). Cognitive measures included Rey Auditory Verbal Learning Test (AVLT), Trail Making Test-B (TMT-B), WAIS Digit Symbol Substitution (WAIS-DSS), and Complex Figure Test (CFT). Linear regression models evaluated the associations between retinal microvascular features and cognitive scores, adjusted for age, sex, and education (Model 1), and additional cardiovascular risk factors (Model 2).

Results: Among all microvascular features, the interocular difference in squared curvature tortuosity within Zone B (all vessels) showed the strongest positive association with AVLT ($p = 0.0021$, Cohen's $d = 0.698$, $\beta = 0.105$, partial correlation= 0.329, 95% CI [0.039–0.170]), robust to cardiovascular risk factors adjustment ($p = 0.0022$, unchanged effect estimates).

Higher tortuosity was associated with better AVLT, suggesting that reduced squared curvature tortuosity may reflect early verbal memory decline. Tortuosity was not associated with TMT-B ($p = 0.425$, Cohen's $d = -0.176$) nor WAIS-DSS ($p = 0.664$, Cohen's $d = -0.096$) nor CFT ($p = 0.664$, Cohen's $d = 0.095$), indicating selectivity for verbal memory. Across all microvascular features that were significantly associated with AVLT, interocular absolute difference achieved larger effect sizes than their single-eye counterparts. Zone B was the most sensitive region for AVLT-related microvascular changes, for both arteries ($p = 0.039$, Cohen's $d = 0.460$) and veins ($p = 0.038$, Cohen's $d = 0.462$).

Conclusions: The interocular asymmetry of squared curvature tortuosity in macula-centered Zone B is a domain-specific biomarker that selectively and robustly associates with verbal memory, outperforming single-eye measurements and independent of executive function, non-verbal memory and processing speed. Interocular retinal microvascular asymmetry is a promising non-invasive approach for verbal memory performance screening and monitoring.

STUDENT POSTER # 182

RETINAL IMAGING BIOMARKERS OF PRECLINICAL ALZHEIMER'S DISEASE: A SYSTEMATIC REVIEW. Rich C, Zheng K, Segovia D, Pitea R, Dumkrieger G, Woodruff B, Dumitrascu O. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) pathology, β-amyloid plaques and tau tangles, begins up to two decades before symptom onset, defining preclinical AD. Current diagnostics (amyloid PET, CSF analysis) are invasive and unsuited to population screening. The retina shares embryological and structural features with the central nervous system, offering a non-invasive window into early neurodegenerative and neurovascular change. Structural OCT, OCT angiography (OCTA), and fundus photography may detect retinal alterations across the AD continuum. We systematically reviewed the literature to identify retinal imaging biomarkers specific to preclinical AD.

Methods: This PRISMA 2020-compliant review searched PubMed/MEDLINE, Embase, Scopus, Web of Science, and Cochrane through March 2026, plus five author-identified studies. Eligible studies enrolled cognitively unimpaired adults with preclinical or high-risk AD defined by molecular biomarkers (amyloid PET, CSF/plasma Aβ, tau) or APOE ε4 status, used a non-invasive retinal imaging modality, and reported quantitative outcomes versus a biomarker-negative or low-risk control group. Reviews, abstracts, and studies restricted to symptomatic AD or MCI were excluded. Two reviewers independently screened and extracted data, resolving discrepancies by consensus; quality was assessed with JBI Critical Appraisal Tools.

Results: Of 884 screened abstracts, 28 studies were included (19 in biomarker-defined preclinical AD; 9 in APOE ε4 carriers), published between 2016–2026 with 15–245 participants, using OCTA (n=13), structural OCT (n=19), and other functional modalities. Foveal avascular zone enlargement was the most consistent OCTA finding (3/5 studies; AUC=0.80). Macular vessel density changes were bidirectional and region-dependent; choriocapillaris perfusion changes appeared in two studies. Structural OCT showed inner retinal layer thinning, more closely linked to tau than amyloid biomarkers. A neuroinflammatory phenotype (thickening, gliosis, inclusion bodies) emerged across five studies, suggesting inflammation precedes neurodegeneration. Functional modalities showed strong single-study associations; the best multimodal model reached AUC=0.97. APOE ε4 carriers showed inner layer thinning and reduced capillary density. Findings were heterogeneous across imaging devices, pipelines, and biomarker definitions.

Conclusions: Retinal imaging shows consistent associations with preclinical AD pathology, though no single parameter yet has sufficient discriminative performance as a standalone biomarker. Multimodal models outperform single-modality approaches. Large-scale, longitudinal, multicenter studies with standardized protocols are needed to validate candidate biomarkers and define retinal imaging's role in population-level AD screening.

STUDENT POSTER # 183

CHARACTERIZATION OF OXIDATIVE STRESS AND MITOCHONDRIAL DYSFUNCTION IN AN SH-SY5Y ALZHEIMER'S DISEASE MODEL USING ROS, JC-1, AND PROTEIN QUANTIFICATION ASSAYS. Richards R III, Clifford A, Ahmetovic A, Bricker S, Conceicao-Larson N, Kay G, Robinson S, David Moses GS, Nural-Guvener H. Grand Canyon University.

Background: Alzheimer's disease is characterized by progressive neurodegeneration associated with oxidative stress and mitochondrial dysfunction. Increased reactive oxygen species production can damage cellular components and contribute to neuronal loss, while impaired mitochondrial membrane potential disrupts cellular energy production and survival. In addition, diabetes-associated glycation pathways have been linked to Alzheimer's disease pathology through the formation of advanced glycation end products and oxidative stress. This study aims to establish and characterize an in vitro oxidative stress model using SH-SY5Y human neuroblastoma cells treated with hydrogen peroxide and glyceraldehyde to investigate cellular mechanisms associated with Alzheimer's disease.

Methods: SH-SY5Y cells were cultured and treated with 65 micromolar hydrogen peroxide or 1.5 millimolar glyceraldehyde for 24 hours. Untreated cells served as negative controls, while 0.15 percent dimethyl sulfoxide served as a vehicle control. Reactive oxygen species production was assessed using the DCFDA Cellular Reactive Oxygen Species Assay. Tert-butyl hydroperoxide was included as a positive control for oxidative stress induction. Mitochondrial membrane potential was evaluated using the JC-1 assay, with carbonyl cyanide-p-trifluoromethoxyphenylhydrazone serving as a positive control for mitochondrial depolarization. Protein extraction and quantification were performed using a bicinchoninic acid assay to establish procedures for future normalization of fluorescence-based measurements.

Results: Preliminary ROS analysis demonstrated treatment-dependent increases in oxidative stress within SH-SY5Y cells. Hydrogen peroxide treatment produced the highest fluorescence signal, while tert-butyl hydroperoxide and glyceraldehyde also increased ROS levels relative to control conditions, supporting successful induction of oxidative stress within the model. Preliminary JC-1 analysis demonstrated successful detection of mitochondrial membrane potential changes across treatment groups. FCCP treatment significantly decreased the JC-1 red-to-green fluorescence ratio (p less than 0.01), confirming mitochondrial depolarization, while hydrogen peroxide treatment significantly altered the JC-1 ratio relative to untreated controls (p less than 0.05). Glyceraldehyde treatment produced measurable but non-significant changes. Representative fluorescence imaging further demonstrated treatment-dependent alterations in mitochondrial polarization. Protein extraction and bicinchoninic acid quantification procedures were successfully established, providing a framework for future normalization of fluorescence-based measurements across treatment groups.

Conclusions: These preliminary findings support the use of SH-SY5Y cells as a model for investigating oxidative stress and mitochondrial dysfunction relevant to Alzheimer's disease. Reactive oxygen species and JC-1 assays successfully detected treatment-dependent fluorescence signals across experimental conditions, demonstrating the feasibility of assessing oxidative stress and mitochondrial membrane potential within this model system. Protein quantification procedures were successfully established and will support future normalization of fluorescence-based measurements to improve quantitative comparisons between treatment groups. Continued optimization and integration of protein-normalized analyses will strengthen future investigations of oxidative stress, mitochondrial dysfunction, and Alzheimer's disease-related cellular pathology.

STUDENT POSTER # 184

LIFELONG IMMUNE EXPERIENCE DRIVES PHENOTYPIC AND FUNCTIONAL MICROGLIAL CHANGES THAT MITIGATE AMYLOID PATHOLOGY IN MOUSE MODELS OF AD. Roscoe D, Fryer J. Mayo Clinic Arizona; Translational Genomics Research Institute; Alzheimer's Consortium.

Background: The immune environment of the brain plays a major role in neurodegenerative conditions such as Alzheimer's disease (AD). The abnormally clean and specific pathogen free (SPF) conditions in which lab mice are typically kept means current mouse models of AD, although not germ-free, lack the normal exposures to diverse commensal and environmental microorganisms that adult humans experience over their lifetimes. By breeding inbred lab mice that have previously experienced exposure to the dirty bedding of pet store mice, we can generate immune experienced (IE) "raised dirty" mice with immune systems that mirror those of adult humans much more closely without undergoing an infection period. While the peripheral immune system effects on such mice have been explored, it is unclear whether these immune effects extend to the brain and whether this plays a role in neurodegenerative disease.

Methods: We exposed APP/MAPT transgenic mice, which accumulate age-dependent amyloid plaque pathology as occurs in AD, to dirty bedding obtained from pet store mice. We bred these mice to establish a line of IE "raised dirty" APP/MAPT mice (along with appropriate controls). At 7 and 12 months, we used pathogen testing to confirm pathogen transfer before collecting brain and spleen for further analysis.

Results: We found that despite increased early (7 months) MOAB-2+ area around amyloid plaques in the brains of IE mice, there were decreased proportions of activated (CD11c+) microglia, and this persisted through 12 months. Immunofluorescence showed increased microgliosis in IE brains, as well as decreased amyloid beta plaque accumulation (MOAB-2+) and disease-associated lysosomal damage (Lamp1+) at 12 months.

Conclusions: In this study, we showed that immune experience from the earliest developmental time point caused both phenotypic and functional changes in microglia which made them better capable of handling AD plaque pathology without showing excessive activation. As humans develop in utero in the context of their mother's experienced immune systems, these changes identified in the microglia of IE lab mice bred in the "raised dirty" method may better model how microglia develop and function in the context of human neurodegenerative disease.

STUDENT POSTER # 185

AGING-LINKED TDP-43 MISLOCALIZATION DRIVES RNA MISPROCESSING. Sailer A, Rhine K. University of Arizona; Arizona Alzheimer's Consortium.

Background: TAR DNA-binding protein (TDP-43) is a predominantly nuclear DNA/RNA-binding protein involved in RNA regulation, splicing, and mRNA stability. Cytoplasmic mislocalization and aggregation of TDP-43 are hallmarks of neuronal aging and neurodegenerative diseases such as Alzheimer's disease. However, mechanisms underlying TDP-43 dysfunction and the cascade of pathological events remain poorly understood. It remains unclear whether dysfunction causes mislocalization or visa versa, and whether aggregation alone is pathogenic.

Methods: To investigate TDP-43 biology in an aging-relevant context, we transdifferentiated fibroblasts from young and old human donors into neurons (tNs). This approach preserved key age-associated markers that are lost in conventional stem cell models, providing a relevant model system for studying TDP-43 dysfunction in aging.

Results: Following confocal immunofluorescence microscopy, CellProfiler-based quantification revealed reduced nuclear localization of TDP-43 in old tNs compared to young tNs, demonstrating aging-linked mislocalization of TDP-43. In addition, Halo-tagged TDP-43 and shRNA constructs were generated to enable TDP-43 overexpression and knockdown, respectively. RNA sequencing following TDP-43 knockdown will be used to identify transcriptomic disruptions associated with TDP-43 loss in young and old tNs and to characterize the RNA pathways most vulnerable to TDP-43 dysfunction. The presence of C-terminal fragments and phosphorylated TDP-43 will be evaluated by Western blot.

Conclusions: By investigating the effects of TDP-43 knockdown as well as the occurrence of TDP-43 truncation and phosphorylation in tNs, our results will provide insight into the molecular mechanisms underlying TDP-43 pathology. Together, these findings will produce a clearer picture of TDP-43 pathology and its contribution to aging and Alzheimer's disease.

STUDENT POSTER # 186

AGING-LINKED NUCLEAR PORE DEGRADATION INHIBITS PROPER RNA TRANSPORT AT THE NUCLEUS. Sakai A, Rhine K. University of Arizona; Arizona Alzheimer's Consortium.

Background: Nuclear pore complexes (NPCs) shuttle cargo to and from the nucleus. Messenger RNA (mRNA) transcribed in the nucleus is bound by RNA-binding proteins (RBPs), forming the messenger ribonucleoprotein (mRNP), which recruits export factors such as NXF1 to shuttle transcripts into the cytoplasm for translation. These complexes are also responsible for recycling these mRNP components back into the nucleus, maintaining RBP proteostasis. NPC proteins are typically long-lived in the cell, with some renewing during mitosis and others persisting through multiple cell cycles. These qualities suggest that NPCs in post-mitotic cells, such as neurons, may be vulnerable, as they do not have the opportunity to renew their NPCs.

Methods: Groups of old and young primary fibroblasts are transdifferentiated into neurons over a three weeks period, preserving aging characteristics that are lost during stem cell reversion. Fluorescence in situ hybridization (FISH) was used to characterize mRNA localization in each neuron age group. Immunofluorescence was used to stain Nups critical to mRNP transport. To further investigate age-associated changes, we plan on using "click-it" RNA tagging to compare RNA dynamics between old and young transdifferentiated neurons. To supplement, RNA-seq and MS will be performed on nuclear and cytoplasmic fractions of aged and young transdifferentiated neurons to determine transcript localizations and protein levels.

Results: Preliminary fluorescence in-situ hybridization data suggests that mRNA in younger neurons localizes to the cytoplasm while older neurons contain more nuclear mRNA. In addition, immunofluorescence of Nup153 and Nup50 in younger and older neurons shows aging-related changes. We hypothesize that aged NPCs will result in lower cytoplasmic levels of mRNA and depleted, damaged, or mislocalized NPC proteins and RBPs.

Conclusions: These findings will illuminate an understudied area of RNA biology, highlighting which elements of the NPC degrade with age, and how the degradation impacts RNA transport.

STUDENT POSTER # 187

MICROGLIAL HOMEOSTASIS AND WHITE MATTER INTEGRITY IN THE FRONTAL CORTEX OF AGED INDIVIDUALS WITH SUPERIOR COGNITIVE ABILITIES. Schafernak-Perez LM, Moreno-Rodriguez M, Mufson EJ, Perez SE. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: There is an exceptional group of very old people (80+ years), termed superagers, whose cognitive abilities are superior to those of age-matched peers and comparable to those of individuals in their fifties and sixties, despite Alzheimer's disease (AD) pathology. Therefore, studying these very old individuals with extraordinary cognition may reveal mechanisms of cognitive resilience. Emerging evidence suggests that neuroinflammation, mediated by astrocytes and microglia, contributes to cognitive decline by altering white matter (WM) and gray matter (GM) integrity, particularly in the frontal cortex (FC), a region involved in episodic memory and vulnerable to AD-related changes.

Methods: Here, we quantitatively investigated glial and myelin integrity in the FC GM and WM of non-demented individuals aged 80 years and older whose episodic memory performance was superior (SCP) to that of normal cognitive performers (NCP) from the Rush Religious Orders Study (RROS). Participants were identified using our recently published psychometric criteria based on the last available Wechsler Memory Scale-Revised Logical Memory Delayed Recall (LM-DR) score obtained prior to death. FC postmortem tissue from 9 NCP and 10 SCP individuals was used to quantify oligodendrocytes (OLIG2), myelin basic protein (MBP), myelin lipid content assessed by Luxol Fast Blue (LFB) staining, microglia (IBA1, TMEM119, and CD68), astrocytes (GFAP), and astrocytic/oligodendrocyte precursor cells (FABP7) using immunohistochemistry and densitometry.

Results: Our findings revealed significantly greater numbers of IBA1-positive microglia, TMEM119-positive resident microglia, and CD68-positive phagocytic microglia in the FC WM, but not in the GM, of SCP compared to NCP individuals. These markers were positively correlated with episodic memory and global cognition scores. In addition, SCP individuals exhibited higher myelin lipid content (LFB) in WM, which was also positively correlated with episodic memory scores.

Conclusions: Together, these findings suggest a critical role for WM integrity and microglial homeostasis in preserving memory function and supporting successful cognitive aging.

STUDENT POSTER # 188

BRAIN DERIVED P-TAU AND PLASMA P-TAU AS BIOMARKERS OF NEUROPATHOLOGY IN ALZHEIMER'S DISEASE: RESULTS FROM AN AUTOPSY COHORT. Shakir S, Denkinger MN, Singh A, Liu J, Dieckhoff K, Hanley D, Marques TM, Monuk E, Stark C, Grill J, Reiman EM, Head E, Ashton NJ. Arizona State University; Banner Sun Health Research Institute; University of California Irvine School of Medicine; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Plasma phosphorylated tau (p-Tau) biomarkers, particularly p-Tau217, show high accuracy for detecting AD pathology. However, plasma p-Tau may be peripherally derived and elevated in other neurological disorders (e.g., ALS). Brain-derived (BD) p-Tau217 is emerging as a promising biomarker in which assay design may improve specificity for AD by selectively binding central nervous system derived tau. Yet, few studies have compared BD and plasma p-Tau variants in distinguishing AD from non-AD. This study compares the diagnostic performance of brain-derived and plasma p-Tau biomarkers in a post-mortem confirmed cohort.

Methods: We analyzed 257 participants from the University of California, Irvine Alzheimer Disease Research Center (mean age 81.1 ± 11.4; 54.9% female) with clinical, plasma, and autopsy data. Age at death, sex, and time between plasma draw and autopsy were controlled. Biomarkers were quantified using Alamar's NULISAseq CNS 120 disease panel and evaluated across neuropathologically defined CERAD plaque and Braak tangle stages. Diagnostic accuracy was assessed using receiver operating characteristic (ROC) area under the curve (AUC). Multi-biomarker models were evaluated.

Results: Differential protein expression revealed brain-derived and total p-Tau217, p-Tau181, and p-Tau231 as most significantly upregulated, driving downstream analyses. BD p-Tau biomarkers, particularly BD p-Tau217 (AUC = 0.94, 95% CI: 0.88–1.00) and BD p-Tau181 (AUC = 0.93, CI: 0.85–1.00), demonstrated strong accuracy in distinguishing neuropathologically-defined AD from non-AD. Pairwise DeLong tests and Benjamini-Hochberg correction confirmed significantly higher AUCs for BD versus total p-Tau181 (padj = 0.013) and p-Tau231 (padj = 0.018). BD p-Tau biomarkers showed significantly stronger correlations with both plaque (p-Tau217, $\rho = 0.63$; p-Tau181, $\rho = 0.60$; p-Tau231, $\rho = 0.59$) and tangle stage (p-Tau217, $\rho = 0.68$; p-Tau181, $\rho = 0.65$; p-Tau231, $\rho = 0.62$) than total p-Tau biomarkers. Steiger's tests confirmed significantly greater associations between BD p-Tau markers and Braak stage (p-Tau217, $z = 4.54$; p-Tau181, $z = 4.16$; p-Tau231, $z = 3.34$; $p < 0.001$) and CERAD stage (p-Tau217, $z = 4.40$; p-Tau181, $z = 5.55$; p-Tau231, $z = 4.60$; $p < 0.001$). Fold-change analyses indicated higher elevations for BD p-Tau217 (3.45) and BD p-Tau181 (3.37) compared with p-Tau217 (2.88) and p-Tau181 (1.84) in AD versus non-AD. LASSO regression analysis revealed that when $\lambda=15$, the model could correctly forecast AD (AUC = 0.989, 95% CI: 0.976-1.00).

Conclusions: BD p-Tau variants, especially BD p-Tau217 and BD p-Tau181, outperform plasma p-Tau, with significantly stronger associations with AD pathology. This supports their potential role as biomarkers in AD research and clinical assessment.

STUDENT POSTER # 189

TAU ACETYLATION DISRUPTS MICROTUBULES HOMEOSTASIS IN ALZHEIMER'S DISEASE MODELS. Sharma B, Tseng JH. Arizona State University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder affecting approximately 7.4 million Americans and is characterized by extracellular amyloid-β (beta) plaques and intracellular neurofibrillary tangles composed of tau. The extent of tau pathology correlates closely with cognitive decline and disease severity, implicating tau dysfunction as a major mediator of neurodegeneration. Under physiological conditions, tau binds and stabilizes axonal microtubules, supporting intracellular transport essential for neuronal function. This interaction is mediated in part by positively charged lysine residues within tau's microtubule-binding domain. Acetylation of these lysine residues neutralizes their charge and may disrupt tau-microtubule interactions, leading to microtubule dysfunction. Aberrant accumulation of acetylated tau species has been identified in AD and other tauopathies, yet the mechanisms by which tau acetylation contributes to neuronal dysfunction remain poorly understood. We hypothesize that acetylation of tau alters microtubule stability and contributes to intracellular transport deficits observed in AD.

Methods: To investigate this, we co-expressed tau with an acetyltransferase (CBP) to induce tau acetylation and assessed markers of microtubule stability in an in vitro cellular model.

Results: Immunoblot analysis revealed that CBP-mediated tau acetylation leads to an increased level of detyrosinated tubulin, a post-translational modification associated with long-lived microtubules that accumulates in AD brains. These findings suggest that tau acetylation disrupts microtubule organization and may impair the structural framework required for efficient intracellular transport.

Conclusions: Together, our results identified a potential mechanism linking pathological tau acetylation to cytoskeletal dysfunction in AD. Understanding how tau acetylation alters microtubule stability may provide new insights into disease pathogenesis and reveal therapeutic strategies aimed at preserving neuronal function and slowing neurodegeneration. Further studies in human neuronal models will determine how tau acetylation affects intracellular transport dynamics and neuronal vulnerability.

STUDENT POSTER # 190

THE EFFECTS OF AGING ON TDP-43 MISLOCALIZATION IN HUMAN NEURONS. Sharma G, Rhine K. University of Arizona; Arizona Alzheimer's Consortium.

Background: Aging is one of the strongest risk factors for neurodegenerative diseases, including Alzheimer's disease. However, the cellular mechanisms that connect aging to disease onset are not fully understood. A major pathological feature of Alzheimer's is the mislocalization of TAR DNA-binding protein (TDP-43), an RNA-binding protein that normally functions in the nucleus but can become depleted and accumulate in the cytoplasm during disease. This nuclear loss can impair RNA processing and contribute to neuronal dysfunction.

Methods: In this project I am investigating aging-related TDP-43 mislocalization using transdifferentiate human neurons, which retain age-associated cellular features more effectively than traditional induced pluripotent stem cell models. The goal of this work is to develop an image-based high throughput assay that can eventually be used to identify compounds capable of restoring the proper TDP-43 mislocalization.

Results: Our preliminary work has established the model system, optimized immunofluorescence staining, developed reliable methods to quantify TDP-43 mislocalization, identified positive control compounds, and miniaturized cell culture on 384-well plates. In particular, we have found that verdiperstat will serve as an internal positive control for the assay.

Conclusions: Once optimized successfully, this assay will support future compound screening and validation studies aimed at identifying potential therapeutic candidates that rescue TDP-43 mislocalization. By building a platform to study aging- associated TDP-43 dysfunction, this project will contribute to a better understanding of Alzheimer's mechanisms and future therapeutic development for age related neurodegenerative diseases. This screening approach may also be extended to other aging-linked diseases or Alzheimer's disease targets.

STUDENT POSTER # 191

ASSOCIATIONS BETWEEN RETINAL VASCULAR MEASURES AND ALZHEIMER'S DISEASE BIOMARKERS. Shen B, Zheng K, Woodruff B, Caselli R, Chen K, Dumitrascu OM. Cornell University; Arizona State University; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Current methods for detecting Alzheimer's disease (AD) pathology using amyloid, tau PET, cerebrospinal or blood fluid testing, can be resource-intensive, invasive, difficult to access, or with further validation. As the retina and brain share developmental, structural and vascular features, retinal imaging offers an inexpensive, non-invasive in vivo complementary approach. However, the association between retinal imaging measurements and established AD biomarkers remains unclear. This study examined whether and what individual retinal imaging measurements are associated with Florbetapir-PET defined amyloid positivity status and with pTau217-defined AD risk groups.

Methods: We analyzed a cohort of 300 cognitively intact individuals who had amyloid-PET, non-mydriatic fundus photography and serologic testing. Sixty-seven retinal vascular metrics were measured from four retinal images per each patient (left and right optic nerve (ON), left and right macula). Amyloid positivity was defined as Centiloid greater than 20. Plasma pTau217 risk was categorized as low risk (less than 0.189), intermediate risk (greater or equal to 0.189 and less than or equal to 0.325), or high risk (greater than 0.325). Logistic regression was used to examine the association between retinal vascular measures and amyloid-positive status, and pTau217 high versus low risk, adjusting for age, APOE4 status, and composite vascular risk (hypertension, diabetes, hypercholesterolemia, or smoking). For each retinal measure, we used a likelihood-ratio (LR) test to compare the full model with all predictors against a reduced model without the retinal measures to assess the retina measure contribution to the prediction. Model performance was assessed using ROC AUC (area under the curve), sensitivity and specificity. False discovery rate (FDR) was applied to account for multiple comparisons.

Results: We analyzed a total of 268 vascular measurements. Out of the 24 vascular measures previously reported, three measures showed significant associations. Left ON average width was associated with amyloid positivity (OR per SD 0.366, change in AUC 0.031, LR p 0.0292; AUC 0.888, sensitivity 1.00, specificity 0.702). High versus low pTau 217 risk was discriminated by the left ON distance tortuosity (OR per SD 6.83, change in AUC 0.148, LR p 0.0029; AUC 0.938, sensitivity 0.833, specificity 0.938) and left ON squared curvature tortuosity (OR per SD 8.61, change in AUC 0.133, LR p 0.0070; AUC 0.922, sensitivity 0.833, specificity 0.938). Among the remaining 244 retina imaging measurements, only the left ON venous distance tortuosity remained significant after FDR correction (OR per SD 732.49, change in AUC 0.190, LR p 4.7×10^{-5}, FDR 0.0126; AUC 0.979, sensitivity 1.00, specificity 0.875).

Conclusions: Optic nerve vascular measures (average vessel width and venous tortuosity) showed significant associations with Florbetapir-PET defined amyloid positivity, and with high pTau217-defined AD risk. Future studies using paired-eye designs, independent cohorts, or multivariable machine learning approaches are needed to identify retinal vascular biomarkers specific to preclinical AD.

STUDENT POSTER # 192

PREDICTING PERSONALISED COGNITIVE DECLINE TRAJECTORIES IN ALZHEIMER'S DISEASE: A PACE-FPCA FRAMEWORK WITH KNOWLEDGE GRAPH REASONING AND AI AGENT INTERFACE. Shiva Prakash S, Pan R. Arizona State University; Arizona Alzheimer's Consortium.

Background: Personalised prediction of cognitive decline in Alzheimer's disease and related dementias (ADRD) is critical for clinical trial stratification, care planning, and patient counselling, yet most existing prognostic tools either rely on population-level averages or fail to account for the irregular, sparse nature of real-world longitudinal assessments.

Methods: We applied Principal Analysis by Conditional Expectation (PACE-FPCA) to 34,101 visits from 7,128 memory clinic patients in the NACC Uniform Data Set, grouped by age (20–40, 41–60, 61–80, and 81+ years) with follow-up ranging from 0 to 19 years. For each patient, integer anchor years (0, 1, 2, etc.) defined forward trajectory windows of up to three years, re-zeroed at presentation. A seven-point grid with 6-month intervals was populated using linear interpolation between observed visits. To improve the estimation of covariance, we used a pairwise-complete approach that incorporated all valid training windows instead of only complete windows, increasing the effective basis from 36 to 10,545 windows in the 61–80 age group. The resulting two-component PACE basis (w_1 representing overall cognitive level and explaining 98.2% of the variance, and w_2 representing rate of decline and explaining 1.8%) was used to score 17,669 anchor windows. To evaluate the contribution of longitudinal history, we generated multiple training samples per anchor using the 0–4 most recent prior visits, producing 46,554 training rows while controlling for disease-stage confounding. A total of 121 features, including clinical snapshot variables, longitudinal history summaries, and cross-modal interaction terms, were used to train a joint-target CatBoost model with MultiRMSE loss, target standardization, and 5-fold GroupKFold cross-validation. Random Forest models were trained on the same feature set for comparison. Finally, all derived information was stored in a Neo4j knowledge graph containing Patient, AnchorWindow, AgeGroupBasis, Feature, and RiskLevel nodes. Relationships included SHAP-weighted feature importance and patient similarity based on k-nearest neighbours.

Results: The joint CatBoost model achieved an R^2 of 0.928 for the first PACE component (w_1) and 0.448 for the second component (w_2) on held-out patients, compared with 0.920 and 0.397, respectively, for independent Random Forest models trained on the same features. The median reconstruction error across 3,121 trajectory windows with at least three future observations was 1.13 MMSE points, which is below the 2.5-point test–retest noise threshold. Cross-modal interaction features accounted for 15.8% of the model's overall importance, with the cognitive domain contributing 5.6% and the functional cognitive discordance feature contributing 1.8%. In contrast, longitudinal history features contributed only 0.5–1.8%.

Conclusions: Once a patient's current cognitive severity is known, the path by which they reached that level provides little additional information about their future rate of cognitive decline. This finding is consistent with previous dementia natural-history studies showing that MMSE trajectories within patients of similar severity are close to a random walk. Current cognitive severity and cross-modal functional–cognitive interactions were the strongest predictors of future decline. A single comprehensive clinical assessment was sufficient to predict a patient's MMSE trajectory over the following two years with a median error of 1.13 MMSE points. The resulting AI agent enables clinical researchers to explore these predictions through natural-language queries, with transparent reasoning linked to knowledge graph relationships and the underlying clinical data, without requiring programming or database expertise.

STUDENT POSTER # 193

DECODING EPIGENETIC HETEROGENEITY IN ALZHEIMER'S DISEASE: DNA METHYLATION SUBGROUPS, PROMOTER BOUNDARY PROTECTION, AND CROSS-TISSUE BIOMARKERS. Shu J, Cheng R, Chen H, Liu L. Arizona State University; Case Western Reserve University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease shows substantial molecular heterogeneity, limiting reproducibility of DNA methylation based biomarkers. DNA methylation is an early and relatively stable mark that can precede pathological and imaging changes, making it a promising early biomarker. However, findings remain inconsistent across cohorts due to variation in cell composition, disease stage, genetic background, and cohort-specific effects.

Methods: Differentially methylated genes were identified using the limma linear regression framework. Functional pathway enrichment was performed using the ClusterProfiler R package. Unsupervised K-means and hierarchical clustering were applied to define subgroups. Subgroup classification signatures were developed using machine learning approache with random forest combined with recursive feature elimination.

Results: We integrated multi-cohort frontal cortex DNA methylation datasets and identified 599 consensus differentially methylated genes enriched in synaptic, immune, and metabolic pathways. Unsupervised clustering identified three reproducible DNA methylation defined Alzheimer's disease subgroups across five independent cohorts, with a 400-probe signature achieving near-perfect classification (AUC greater than 0.99). These subgroups exhibited distinct biological profiles strongly influenced by cell type composition, particularly neuronal to glial balance. Cluster 1 showed the highest neuronal to glial ratio consistent with neuronal preservation, whereas Cluster 2 showed marked neuronal depletion and glial enrichment. Cluster 2 was enriched for APOE2, while Cluster 3 was enriched for APOE4, indicating genetic epigenetic interactions in subgroup formation. Functional enrichment analyses indicated distinct states of synaptic maintenance, inflammatory activation, and metabolic mitochondrial adaptation. Integrating global and subgroup specific signatures improved Alzheimer's disease classification in independent validation cohorts (AUC greater than 0.94). Brain-to-blood analyses demonstrated partial preservation of subgroup patterns in peripheral methylation profiles, enhancing translational applicability. At the mechanistic level, MB-41–associated promoter boundary protection was identified as a potential regulator of epigenetic stability, and its disruption may contribute to aberrant methylation spreading in Alzheimer's disease–related pathways.

Conclusions: AD epigenetic variability is structured, driven by cell composition, genetic risk, and promoter boundary integrity. This framework resolves methylation inconsistencies and enables subgroup-informed biomarkers, with MB-41 mechanism and brain-to-blood translational potential.

STUDENT POSTER # 194

INFLUENCE OF EXERCISE ON WESTERN DIET INDUCED NEUROLOGICAL AND BEHAVIORAL CHANGES. Siegel MM, Nenni JA, Beyazyildirim M, Isa AM, Al-Nakkash L. Midwestern University; Arizona Alzheimer's Consortium.

Background: Chronic consumption of high-fat and high-sugar (HFHS) diet promotes a pro-inflammatory state that can impair normal nervous system function, increasing the risk of neurodegenerative disorders such as Alzheimer's disease (AD). Growing evidence suggests that diet-induced inflammation may contribute to the pathological processes associated with AD. Diet and exercise interventions have long been utilized to counteract the detrimental effects of HFHS dietary patterns, in part by reducing systemic inflammation and mitigating the pro-inflammatory environment induced by excessive fat and sugar intake. Our study aims to investigate how manageable lifestyle variables of a lean diet and exercise ameliorate the underlying HFHS-diet-related neurological changes that underlie diseases like AD.

Methods: Five-week-old male C57BL/6 mice were separated into the following four groups for a 12-week treatment period: lean diet with normal water and sedentary activity level (Ln-Sed, n=10), lean diet with normal water and exercise (Ln-Ex, n=10), HFHS diet and sedentary activity level (HFHS-Sed, n=10), and HFHS and exercise (HFHS-Ex, n=9). The high-fat diet included 60% fat content pellets, and the high-sugar water consisted of a 42 g/L (55% fructose/45% sucrose) solution. Exercised mice ran on a treadmill 5 days/week (150 min/week) from week 3 to 12. Body weight (BW, g) was measured weekly. Behavioral assessments, including the open field test (OFT) and novel object recognition test (NORT), were conducted to evaluate locomotor activity, anxiety-like behavior, and cognitive function. Hippocampus tissue samples were analyzed by Eve Technologies to assess cytokine levels.

Results: Compared to Ln-Sed mice, the final body weight (BW) of Ln-Ex mice was 10% less (mean: 31.86g, $p < 0.05$ for both changes). Additionally, compared to Ln-Sed mice, Ln-Ex mice had increased perimeter/decreased center time and reduced center/periphery-entry/exits ($p<0.05$).

Conclusions: The findings of this study demonstrate HFHS diet induced significant body weight gain compared to lean controls and that exercise attenuated body weight gain. These weight changes were associated with notable behavioral differences. Behavioral changes indicated that exercise positively influenced total ambulatory activity by rescuing the decreased locomotion exhibited by HFHS-sedentary mice (i.e., compared to Ln-Sed mice). However, exercise also increased anxiety-like behavior as evidenced by the data for Ln mice in the OFT and both Ln and HFHS mouse groups in the NORT. In addition to showing alterations in anxiety levels, the behavioral results of this study may also demonstrate that there are additional changes in memory of mice that exhibited altered NORT preference index scores. Future research will explore these behavioral changes associated with diet and activity and the potential relationship to concomitant hippocampal cytokine alterations and memory-related consequences.

STUDENT POSTER # 195

CATHEPSIN ACTIVITY AND DETECTION OF MRNA VARIANTS IN NEURAL CELLS. Sodhi AA, Younglove B, Uppalapati CK, Harrison, AM, Hull EE, Leyva KJ. Midwestern University; Arizona Alzheimer's Consortium.

Background: Both progranulin (PGRN) and cathepsins have been implicated in neurodegenerative diseases. Dysregulated lysosomal function, particularly abnormal production or processing of cathepsins, contributes directly to neurodegeneration, and therapeutic strategies aimed at restoring lysosomal activity have shown promise in several Alzheimer's disease (AD) models. Despite this progress, the mechanistic relationships among PGRN, lysosomal function, and inflammation remain poorly defined, limiting advancement of targeted therapeutics. A critical knowledge gap exists regarding how inflammatory cytokines modulate cathepsin activity and how these changes influence PGRN processing. Addressing this gap is essential for identifying therapeutic strategies capable of preserving lysosomal integrity and cognitive function in AD. The proposed study aims to evaluate the effects of PGRN and cytokine signaling on both microglial and neuronal cells. Our hypothesis is that cathepsin activity and/or mRNA variants are produced in response to inflammatory stimuli, which may alter lysosomal function and affect PGRN processing, resulting in pathology associated with AD.

Methods: Cathepsin L (CTSL) and cathepsin D (CTSD) activity was measured using a fluorometric assay on cell lysates from cytokine-treated (pro-inflammatory or anti-inflammatory) and untreated murine Neuro-2a and SIM-A9 cells under three conditions: without addition of PGRN, addition of PGRN 24 hours prior to cytokine treatment, and addition of PGRN 24 hours after cytokine treatment. RT-PCR was performed using combinations of specific CTSL and CTSD primers to identify CTSL or CTSD mRNA splice variants expressed, and results were analyzed using gel electrophoresis. Immunohistochemistry (IHC) was performed on fixed brain tissue samples from normal and AD patients using anti-CTSD and anti-CTSL antibodies to determine cathepsin expression in conjunction with anti-p-Tau to determine co-localization.

Results: Cytokine treatment significantly decreased CTSL and CTSD activity in SIM-A9 cells but did not have a significant effect on Neuro-2a cells. In contrast, previous work showed pro-inflammatory cytokines increased CTSL activity in a human microglial cell line. PCR analysis shows evidence of differential splicing of cathepsin mRNAs with respect to PGRN and/or cytokine treatment. IHC results suggest that CTSL & CTSD protein expression is higher in tissues from AD patients compared to normal tissues, and that both CTSL and CTSD appear to be co-localized with p-Tau.

Conclusions: Preliminary data suggest differential expression of CTSD & CTSL, which may impact PGRN activity, occurring in the context of inflammation or disease. Future research will focus on isolating and sequencing CTSL and CTSD mRNA splice variants to determine any correlation between mRNA, inflammation, and protease activity in pathology of AD. Our results will serve as a foundation for determining if CTSD & CTSL expression and/or activity can be controlled by differential RNA processing, thus may offer potentially new therapeutic strategies focused on preventing or slowing the early progression of Alzheimer's disease and other neurodegenerative conditions.

STUDENT POSTER # 196

APPLICATION OF GRAPHS TO IDENTIFY BIOMARKERS USING HUBS AND FUNCTIONAL CONNECTIVITY TO ASSESS DISEASE PROGRESSION IN ALZHEIMER'S DISEASE WITH FMRI AND PET. Steele M, Wu T, Pan R. Arizona State University; Arizona Alzheimer's Consortium.

Background: The graph models of the brain provide metrics for identification of new biomarkers structurally and functionally. An atlas and functional network can be combined to identify regions of interest with clusters of high functional connections that change during progress of the disease for three stages: normal, mild cognitive impairment (MCI), and Alzheimer's Disease (AD). A literary review suggests precuneus and posterior cingular cortex (PCC) are central connectome hubs in the brain. The precuneus and PCC are regions of interest (nodes) in the Default Mode Network (DMN). This study asserts the following hypotheses:
Hypothesis 1: Amyloid Beta Plaques accumulate at hubs with more structural or functional connections in progression of MCI to AD and biomarkers exist in DTI, fMRI and PET to support the hypothesis.
Hypothesis 2: Tau strands accumulate at hubs with more structural or functional connections in progression of MCI to AD and biomarkers exist in DTI, fMRI and PET to support the hypothesis.

Methods: Medical imaging data from ADNI is used to identify patients with both fMRI and PET scans. The fMRI data is preprocessed and mapped to an AAL90 SPM 12 and registered to MNI space. The intermediate data is converted to a 90 by 90 graph matrix for the first ninety regions. Each ROI is mapped to a functional network defined by Yeo 7. The fMRI data is then merged with concurrent PET scans with SUVR data using ADNI subject IDs.

Results: The results show that in normal stages, the hubs cluster in the somatomotor network with a baseline level of connections in fMRI and low level of amyloid and tau proteins accumulating in the PET images. As the disease progresses to MCI, the baseline amyloid and tau SUVR values increase, and the number of functional connections expands to compensate for the proteinopathy. In Alzheimer's Disease, the tau and amyloid proteins are elevated in SUVR, and the cluster of hubs with high connectivity changes to the Visual and Limbic Networks. The amyloid beta plaques correlate negatively with global connection metrics. However, the pathology correlates positively with local, tight clusters in residual regions of interest such as in the DMN.

Conclusions: The pattern shows an adaptation of the brain's functional network to adjust for the impacts of the neurodegenerative disorder which leads to fragmented reorganization. The preliminary data analysis must be cross-validated with OASIS-3 data. A subject matter expert in pathology for medical imaging data must be added to confirm methodology and analysis.

STUDENT POSTER # 197

RESOLVING ENDOGENOUS AUTOFLUORESCENCE TO ENABLE MULTIMODAL SPATIAL PROFILING OF POST-STROKE NEUROINFLAMMATION IN AGED HUMAN BRAIN. Stewart A, Begay K, Biswas D, Yeoh-Baxter W, Serrano G, Lorenzini I, McHattie R, Doyle K. University of Arizona, Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Stroke survivors face substantially elevated long-term risk of neurodegenerative decline, yet the neuroinflammatory mechanisms linking chronic post-stroke injury to this progression remain poorly defined in human tissue. Spatial profiling of immune and inflammatory microenvironments in aged brain tissue from stroke survivors is critical for understanding chronic pathology. While fluorescence-dependent methods are commonly employed, endogenous autofluorescence, often attributed to lipofuscin, is a recognized confounder. However, multiple endogenous fluorophores with overlapping excitation and emission spectra in formalin-fixed paraffin-embedded (FFPE) tissue may contribute substantially to background signal across imaging channels. This cumulative impact in aged brain tissue remains incompletely defined, constraining effective spatial biology implementations.

Methods: We evaluated endogenous autofluorescence in FFPE brain tissue from the Banner Sun Health Research Institute Brain and Body Donation Program (donors aged 71 to 89 years, postmortem intervals less than 3 hours). Endogenous autofluorescence was first quantified in stained tissue using widefield epifluorescence microscopy to establish baseline background signal (Phase I). Fluorescently-tagged antibodies were then evaluated by widefield epifluorescence followed by confocal microscopy in selected cases to assess spectral separation (Phase II). To characterize the endogenous spectral peaks preventing antibody signal separation, unstained tissue was screened by widefield epifluorescence followed by confocal multi-channel and lambda analysis in selected cases (Phase III). Images were analyzed using custom FIJI macros and R-based statistical pipelines. In parallel, systematic literature review identified biological sources underlying observed spectral peaks, yielding a database of 10 impactful endogenous fluorophores from 219 publications.

Results: Quantitative analysis revealed that 60 percent of antibody-based fluorescence measurements fell within background noise thresholds. Literature synthesis identified dominant autofluorescence contributors, including lipofuscin, ceroids, collagen IV and elastin in vascular basement membranes, porphyrins, heme, advanced glycation end-products, and metabolic fluorophores NADPH, NADH, and FAD. These sources exhibited broad spectral overlap with commonly used immunofluorescence antibodies, obscuring signal.

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STUDENT POSTER # 198

ACCELERATED AGING IN THE ALZHEIMER'S DISEASE (AD) BRAIN: APPLICATION OF NEURAL NETWORK MODELS TO STRUCTURAL MRI DATA QUANTIFIED USING FREESURFER 8. Su CW, Sohankar J, Luo J, Li S, Su Y, Wu T, Chen K. Arizona State University; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Structural Magnetic Resonance Imaging (T1-MRI) data have been used for early diagnosis or biomarker identification of Alzheimer's disease (AD). Recently, FreeSurfer 8 became available as an upgraded tool to quantify and analyze MRI data utilizing SynthSeg 2.0 for faster segmentation, and the accuracy of this new method in brain age prediction models has yet to be investigated. In this study, we investigated the efficacy of the new FreeSurfer 8 quantified MRI data in neural network models for age prediction.

Methods: All MRI scans were processed using FreeSurfer version 8.1 with SynthSeg 2.0. A total of 3,846 scans from cognitive unimpaired (CU) individuals at each visit from the National Alzheimer's Coordinating Center (NACC) were used for model training for age prediction, with the brain age gap (BAG) calculated as the difference between the chronological age and the predicted age. The model was trained using a multi-layer perceptron (MLP) with 3 hidden layers and a Gaussian Error Linear Unit (GELU) activation followed by normalization and dropout rate of 20%. The model was further tested in all scans from NACC (N = 7,292) and cross-cohort evaluation with data from ADNI (Alzheimer's Disease Neuroimaging Initiative, N = 15,043). The datasets included subjects at various stage of AD characterized by the Clinical Dementia Rating (CDR) with values of 0, 0.5, 1, 2, and 3. The correlation between CDR and BAG at the time of visit was used to investigate accelerated aging in AD. We also evaluated how different brain regions contribute to predicted and accelerated aging by grouping the 101 FreeSurfer defined regions into 12 broader neuroanatomical classes and performing permutation importance analysis over them.

Results: Within the training dataset, the model achieved a Mean Absolute Error (MAE) of 4.71. The internal evaluation from all data within NACC resulted in an MAE of 4.79, and an MAE of 6.07 for those scans from impaired individuals only. The external evaluation with ADNI resulted in an MAE of 4.99, suggesting consistent age prediction accuracy of the model over different cohorts. The linear mixed effects model showed a highly significant positive association ($p < 2e\text{-}16$) between BAG and CDR level. From the feature importance analysis, the ventricles and cerebral spinal fluid (CSF) class was consistently the most important across both cohorts.

Conclusions: The results suggest that by leveraging the data processed by FreeSurfer 8 with SynthSeg 2.0, our model can reliably be used for the prediction of normal and accelerated brain aging in AD. Additionally, the feature importance analysis points towards brain regions such as ventricles and CSF for further study in brain aging.

STUDENT POSTER # 199

NEURONAL AGING AND STAU1-ASSOCIATED RNA TRANSPORT. Sun P, Rhine K. University of Arizona; Arizona Alzheimer's Consortium.

Background: Neurons depend on long-range RNA transport to support local protein synthesis at distant synapses. This process is mediated by RNA-binding proteins (RBPs), which assemble into ribonucleoprotein (RNP) granules that regulate RNA localization, stability, and translation. Among these RBPs, Staufen double-stranded RNA-binding protein 1 (STAU1) plays a central role in mRNA transport, translation, and decay. However, whether aging alters STAU1 localization and its associated RNA transport pathways remains unclear.

Methods: Human transdifferentiated neurons (tNs), which retain donor age-associated signatures, were used to investigate age-dependent changes in STAU1. STAU1 localization was compared between neurons derived from young and old donors using immunofluorescence microscopy. To examine the mechanisms and consequences of altered STAU1 localization, we generated a STAU1-Halo fusion construct for live granule visualization, developed STAU1-targeting shRNA for loss-of-function studies, and established a synaptic-enriched fractionation workflow to support downstream RNA sequencing and protein profiling.

Results: Preliminary immunofluorescence analysis revealed an age-associated redistribution of STAU1 in human transdifferentiated neurons. Neurons derived from young donors exhibited prominent STAU1 puncta within distal neuronal processes and synaptic-enriched regions, whereas neurons derived from old donors showed reduced peripheral STAU1 localization. These findings suggest a loss of distal STAU1 enrichment during neuronal aging. In parallel, STAU1-Halo, STAU1 shRNA, and synaptic-enriched fractionation platforms were successfully established to enable future analyses of STAU1-dependent RNA transport and synaptic molecular composition.

Conclusions: Our findings identify age-associated changes in STAU1 localization as a potential early feature of neuronal aging. The experimental platforms established here provide a framework for testing whether STAU1 dysregulation contributes to impaired RNA transport and altered synaptic RNA and protein composition. Together, these studies position human transdifferentiated neurons as a tractable model for investigating RNA transport mechanisms during neuronal aging.

STUDENT POSTER # 200

SPATIAL MEMORY PRECISION AND NEUROPSYCHOLOGICAL PERFORMANCE IN OLDER ADULTS. Sutherland S, Millmond E, Ekstrom A, Hill P. University of Arizona; Arizona Alzheimer's Consortium.

Background: Traditional neuropsychological memory measures often rely on categorical outcomes, such as correct versus incorrect recognition, which may miss subtle differences in the fidelity of retrieved details. Continuous memory paradigms address this limitation by separating whether information was successfully retrieved from how precisely it was remembered. In the Continuous Item Location Task, or CILT, participants study objects at locations around a circular display and later reconstruct each object's remembered location. The present study examined whether CILT retrieval success and retrieval precision show similar or distinct associations with standard neuropsychological domains in older adults.

Methods: One hundred ten cognitively characterized older adults between 62 and 87 years of age, including 91 cognitively unimpaired participants and 19 participants with mild cognitive impairment, completed a neuropsychological test battery assessing verbal memory, visual memory, executive functioning, and visuospatial ability. Participants also completed the CILT. Trial-wise angular errors were fit with a probabilistic mixture model to estimate retrieval success, reflecting the probability of a successful memory-based response, and kappa, a memory precision estimate that captures the dispersion of distance errors among successful retrieval trials. Associations between neuropsychological domain scores and CILT retrieval success and memory precision were examined using correlations with Bonferroni correction for eight comparisons. Group differences by cognitive status were examined using Welch independent-samples t tests.

Results: Group comparisons showed that participants with mild cognitive impairment had significantly greater angular distance error than cognitively unimpaired participants, whereas group differences in retrieval success and memory precision did not reach significance. Because angular distance error was highly related to retrieval success, correlations focused on the two model-based CILT outcomes: retrieval success and memory precision. After Bonferroni correction for eight comparisons, retrieval success was significantly associated with verbal memory and visual memory. Associations between retrieval success and executive functioning or visuospatial ability were not significant after correction. In contrast, memory precision was not significantly associated with any neuropsychological domain after correction.

Conclusions: CILT retrieval success and retrieval precision showed distinct relationships with standard neuropsychological measures, with verbal and visual memory associated with successful retrieval but not memory precision. These findings suggest that model-based memory precision may capture aspects of spatial memory performance not fully represented by traditional neuropsychological assessments.

STUDENT POSTER # 201

ELEVATED ITSN1 AS A LINK BETWEEN ENDOSOMAL DISRUPTION AND NEURODEGENERATION IN DOWN SYNDROME AND ALZHEIMER'S DISEASE. Tallino S, Newbern J, Velazquez R. Arizona State University; Arizona Alzheimer's Consortium.

Background: Endosomal dysfunction is increasingly implicated in neurodegeneration, but mechanisms linking altered endocytic regulation to cellular vulnerability remain unresolved. In Down syndrome (DS), individuals exhibit hallmark Alzheimer's Disease (AD) pathology by age 40, preceded by early cellular abnormalities including endosomal enlargement and intracellular amyloid accumulation. In both DS and AD, the basal forebrain (BF) shows volume loss via imaging and cholinergic neuron loss in post-mortem tissue that correlates with cognitive decline. The Ts65Dn mouse model of DS also exhibits loss of BF cholinergic neurons (BFCNs), which demonstrate enlarged early endosomes with age as Aβ accumulates. Intersectin 1 (ITSN1), a scaffolding-associated protein integral to endosomal trafficking, has been suggested as a modulator of these events as it is triplicated in DS and elevated in AD. Further, perinatal dietary interventions that prevent BFCN decline in Ts65Dn mice reduce ITSN1 levels and restore early endosome size in BFCNs. The goal of this project is to determine the role of ITSN1 in the context of endosomal enlargement and cell loss in Ts65Dn mice.

Methods: We first assessed ITSN1 expression as part of a genome-wide mRNA microarray screen in human AD (n = 97) versus age-matched controls (n = 98), balanced for sex; we also investigated protein-level expression of ITSN1 in BF homogenates from 8mo old Ts65Dn mice (n = 12 animals/genotype, sex balanced). We then investigated whether adeno-associated virus (AAV)-mediated delivery of an ITSN1-targeting short hairpin RNA (shRNA) in the adult BF prior to the onset of BFCN loss would be sufficient to prevent endosome enlargement, BFCN loss, and BFCN-dependent behaviors. We stereotactically injected the AAV.PHP.eB serotype carrying GFP and either a scrambled sequence (AAV-scrmbl) or the ITSN1 shRNA (AAV-shITSN1) into the medial septum of the BF at 3.5mo old (n = 8-14 per sex, genotype, and virus). BF-modulated behaviors were tested at 11mo old, and tissues were subsequently collected for immunohistochemical and other analyses at 11.5mo.

Results: We found significantly elevated ITSN1 expression in individuals with AD compared to age-matched controls, as well as significant elevation of ITSN1 in the BF of Ts65Dn mice. Preliminary results suggest AAV-mediated reductions of ITSN1 in the BF of AAV-shITSN1 mice relative to controls. Notably, AAV-shITSN1 mice showed slight but significant improvements in rotarod performance and completed more correct trials in the radial arm water maze, with additional analyses ongoing to determine if ITSN1-mediated endosomal alterations coincide with these behavioral improvements.

Conclusions: Understanding the contribution of ITSN1 to endosomal homeostasis may provide insight into early pathological events that are common to both AD and DS and may inform future cognition-relevant therapeutic targets.

STUDENT POSTER # 202

AGE RELATED CHANGES IN COGNITIVE FUNCTION AND STRUCTURAL BRAIN CONNECTIVITY STUDIED VIA DIFFUSION MRI. Teluguntla K, Ugonna C, Wiskoski H, Matijevic S, Ryan L, Chen N, Trouard T. University of Arizona; Arizona Alzheimer's Consortium.

Background: Magnetic resonance imaging (MRI) serves as an invaluable, non-invasive method for investigating the macrostructural and microstructural properties of the human brain. These imaging techniques are critical for evaluating healthy cognitive aging as well as pathological processes such as dementia. As individuals age, structural connectivity within the brain may undergo alterations that can impact cognitive function. This study evaluates whole-brain structural connectivity through diffusion MRI (DMRI), and investigates the relationships with advancing age and cognitive performance.

Methods: The study utilizes structural T1-weighted MRI and multi-shell many-direction DMRI in 228 participants, 50 to 80 years old. Using MRtrix3 software, white matter fiber orientation distribution (FOD) functions were calculated using Constrained Spherical Deconvolution (CSD) from which whole-brain tractograms were generated to model white matter tracts. Using FreeSurfer and the structural T1-weighted MRI, gray matter was parcellated into 84 distinct regions of interest. A comprehensive connectivity matrix was then generated by calculating the structural connectivity strength between each gray matter region, capturing both intra-hemispheric and inter-hemispheric connections. From the connectivity matrix, we investigated five graph theory-derived network metrics reflecting both network integration (global efficiency and path length) and segregation characteristics (modularity, clustering coefficient, and local efficiency).

Results: Statistical analysis evaluating the network measures against subject age revealed significant correlations. Analysis of the integration measures showed that global efficiency significantly decreased with age ($p=0.00026$), while structural path length significantly increased with advancing age ($p=3.7e-5$). Regarding segregation measures, both the clustering coefficient and local efficiency exhibited significant decreases with age ($p=0.0003$, $p = 0.016$, respectively). Modularity showed no significant association with age.

Conclusions: The findings of this study demonstrate that structural connectivity measures of the human brain can be effectively and non-invasively quantified using DMRI. The significant correlations observed between advancing age and alterations in five distinct network measures suggest that structural connectivity may be sensitive to the physiological changes in the brain that occur in aging. Future work will focus on elucidating how individual network connectivity measures directly relate to specific cognitive processes, as well as investigating the influence of demographic factors, such as sex and ethnicity, on structural connectome-derived network measures.

STUDENT POSTER # 203

MONTE CARLO VALIDATION OF DITSI: A NOVEL FRAMEWORK FOR CHARACTERIZING BRAIN MICROSTRUCTURE VIA DOUBLE DIFFUSION ENCODING MRI. Trinate R, Galinsky V, Frank L, Hutchinson E. University of Arizona; University of California San Diego; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder in which clinical symptoms typically appear only after substantial neuronal damage has occurred. The conventional diffusion MRI, single diffusion encoding (SDE) methods lack sufficient specificity to detect early AD microstructural changes because they are insensitive to microscopic anisotropy. Double diffusion encoding (DDE) overcomes some of these limitations by encoding correlations between water displacements in two gradient blocks. The recently developed Diffusion Tensor Subspace Imaging (DiTSI) framework represents the DDE signal by separating radial and angular components of the spin density function. However, systematic validation of DiTSI metrics across different acquisition parameters and tissue geometries is needed. The objective of this work is to validate the DiTSI framework using Monte Carlo simulations by assessing sensitivity to various tissue geometries — including different axon sizes, crossing fibers, and size distributions — via DiTSI metrics RA, SA, Rvar, and Svar.

Methods: Monte Carlo simulations were performed using DifSim with 3D models of: coherent fibers of different radii, binomial size distributions, normally distributed size heterogeneity, and crossing fibers. The 3D models were created by blender 2.93 and Matlab2025b. DDE pulse sequence parameters were: b-values of 1000, 2000, 4000 s/mm², 9 b-value pairs, $\delta_1 = \delta_2$ = 1–5 ms, $\Delta_1 = \Delta_2$ = 100 ms, τ_m = 0 ms. Direction subsets of 6, 9, 12, 20, and 50 were evaluated to determine the minimum stable acquisition.

Results: A stability for directional sampling was identified at 20–30 directions. Sampling below 12 directions caused significant reconstruction artifacts, whereas 20 directions provided reliable metrics suitable for optimized clinical protocols. DiTSI effectively differentiated axon calibers across 1–11 μm, demonstrating clear sensitivity to axon size. In heterogeneous tissue environments the Rvar pattern differed from other geometries, and RA increased linearly with increasing heterogeneity, confirming that the framework correctly captures ensemble microstructure in non-uniform environments — supporting its utility in AD tissue with heterogeneous pathology. For crossing fiber geometries, a sinusoidal response in SA and RA across crossing angles confirmed high angular resolution and DiTSI's ability to disentangle multiple fiber populations within a single voxel.

Conclusions: This study validates the DiTSI framework using Monte Carlo simulations across coherent, heterogeneous, and crossing fiber geometries. A minimum of 20 directions is required for stable reconstruction. DiTSI is sensitive to axon radius and robust against size heterogeneity — features critical for detecting early axonal pathology in AD. These findings support DiTSI as a promising non-invasive biomarker for tissue microstructure characterization. Future work will validate these findings with ex vivo DDE MRI data and compare DiTSI with advanced frameworks including NODDI and MAP-MRI.

STUDENT POSTER # 204

MATRIN 3 MODULATION OF M6A LEVELS AS A NOVEL MECHANISM OF NEURODEGENERATION. Valentine AD, Quezada G, Zayas Abril A, Bagga I, Bakkar N, Bowser R, Medina DX. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: N6-Methyladenosine (m6A) is a dynamic post-transcriptional RNA modification that plays a key role in RNA splicing, translation efficiency, and decay. Recently, m6A dysregulation has been implicated in neurodegenerative diseases including Amyotrophic Lateral Sclerosis (ALS) and Alzheimer's Disease (AD). mRNA is methylated via the "writer" complex consisting of methyltransferases METTL3 and METTL14 and demethylated via "erasers" such as FTO or ALKBH5. Although this process is known to be altered in a variety of diseases, its dysregulation and contribution to disease progression is poorly understood. Previously, RNA binding proteins (RBP) have been shown to regulate this process by facilitating "writer" complex formation and binding of m6A-methylated transcripts. One such RBP, matrin 3 (MATR3), has been linked to sporadic and familial forms of neurodegeneration. Matrin 3 is a highly conserved nuclear RBP that regulates post-transcriptional RNA processing, alternative splicing, and mRNA export. We aim to identify if matrin 3 contributes to neurodegeneration by regulating m6A RNA methylation in neuronal cells. Specifically, we hypothesize that matrin 3 loss-of-function (LOF) leads to neurodegeneration due to loss of m6A homeostasis.

Methods: This study took an in vitro approach by utilizing the motor neuron (MN)-like cell line NSC-34. MATR3 gene silencing was conducted with siRNA, while either wild-type (WT) or LOF mutant (S85C) matrin 3 protein was overexpressed via plasmid. Coimmunoprecipitation assays were then performed on the lysates after matrin 3 level manipulation by using magnetic beads and antibodies specific to matrin 3 and the "writer" proteins METTL3 and METTL14. Quantitative immunostaining was performed to measure how matrin 3 pathology could affect m6A levels and the distribution m6A pathway members in different subtypes and regions of the central nervous system (CNS) in ALS, FTD, and AD. Matrin 3 subcellular localization was assessed in several areas of the brain, including frontal cortex, motor cortex, and entorhinal cortex.

Results: Upon matrin 3 gene silencing, m6A levels decreased, "writer" levels remained unaffected, and "eraser" levels increased. Furthermore, METTL3 and METTL14 binding was hindered by matrin 3 knockdown. Upon WT matrin 3 overexpression, m6A and "writer" levels remained the same as the control, but "eraser" levels decreased. Matrin 3 S85C overexpression resulted in decreased m6A levels, no change in "writer" levels, and an increase in "eraser" levels. WT matrin 3 overexpression did not affect METTL3-METTL14 binding; however, matrin 3 S85C overexpression decreased METTL3-METTL14 binding.

Conclusions: The data suggest matrin 3 directly influences and facilitates "writer" complex formation in neuronal cells, and that matrin 3 LOF results in hypomethylation of RNA. Further, we hypothesize that the matrin 3 S85C mutation, the most common matrin 3 mutation associated with ALS, could weaken its ability to heterodimerize METTL3 and METTL14, resulting in m6A loss. As such, the results provide a deeper insight into the relationship between matrin 3 and m6A in the context of neurodegeneration. Next steps will involve evaluating METTL3-METTL14 heterodimerization in 3D space through immunofluorescence in the presence of LOF matrin 3, as well as performing RNA sequencing on matrin 3 knockdown and METTL3 knockdown RNA to identify differentially expressed genes associated with both loss of matrin 3 and m6A. Future studies will explore the use of FTO inhibitors to reverse hypomethylation and evaluate its effects on neuronal health.

STUDENT POSTER # 205

UNRAVELING THE LINK BETWEEN AUTISM AND PARKINSONISM: INTEGRATING CLINICAL PHENOTYPES WITH CUMULATIVE GENOMICS. Velez M, Harker S, Ofori E, Lewis C, Peterson D, Belnavis A, Rush M, Davila E, Phan E, Ingram L, Gallegos S, Venkatesh H, Smith-Plata J, Strasia S, Black J, Braden BB. Arizona State University; Arizona Alzheimer's Consortium.

Background: Autism spectrum disorder (ASD) is a lifelong neurodevelopmental condition, yet aging in autistic adults remains understudied. Emerging evidence suggests autistic adults experience elevated risk of parkinsonism symptoms and Parkinson disease (PD) compared to non-autistic adults. However, studies using self-report and medical records provide limited insight into the clinical and genetic mechanisms linking ASD and PD.

Methods: Participants were enrolled in a larger longitudinal cognitive and brain aging study. PD polygenic scores (PD-PGS) were generated for 73 autistic adults (44% women; diagnoses confirmed via ADOS-2) and 75 non-autistic controls (mean age=43.9(±17) 18-83) using PRSice-2 and summary statistics from a PD genome-wide association study (Jiang et al., 2021). Single nucleotide polymorphisms surviving clumping were retained at p=0.001. Linear regression models examined group differences while controlling for sex interactions and the first 10 ancestry principal components. In a subsample of 27 participants (autistic: 14; non-autistic: 13; age=51.74(±14.27); range: 24-78), parkinsonism symptoms were evaluated using Movement Disorders Society-Unified Parkinson Disease Rating Scale Part III (MDS-UPDRS III) total scores administered by certified raters blinded to diagnostic group. Group differences were examined using independent-samples t-tests.

Results: Autistic adults had significantly larger PD-PGS compared to non-autistic adults ($t(134)=2.98$, $p=0.003$). Autistic adults also demonstrated significantly greater parkinsonism symptom severity on the MDS-UPDRS III relative to controls ($t(25)=-2.46$, $p=0.021$), with a large effect size (Cohen $d=0.98$).

Conclusions: These findings provide converging clinical and genomic evidence that autistic adults may exhibit elevated parkinsonism symptoms and increased genetic liability for PD relative to non-autistic adults. Although replication in larger cohorts is needed, these findings underscore the importance of monitoring motor function in autistic adults across the lifespan and highlight the value of integrating clinical and genomic approaches to improve early detection and intervention efforts.

STUDENT POSTER # 206

FROM ONE READER TO MANY: A MULTI-AGENT VISION-LANGUAGE FRAMEWORK FOR RETINAL IMAGING SCREENING OF ALZHEIMER'S-ASSOCIATED ABNORMALITY. Wang V, Dumitrascu O. Brophy College Preparatory; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) retinopathyhas subtle signals in color fundus photographs (CFP). Given absent obvious AD-specific markers, a direct single-pass AI model could miss subtle vascular or quality-impaired lesions, and innacurately default to a "normal" classification. Inspired by hospital practice, where specialists with different expertise combine judgments on the same case, we tested whether a multi-agent vision-language design could surface these signals by separating image interpretation into clinically inspired roles: quality assessment, lesion inspection, vascular density and vascular pattern analysis, followed by final aggregation. Our project's long-term goal is the development of a scalable, noninvasive retinal-based screening model for early AD risk detection.

Methods: We analyzed a filtered UK Biobank dataset of 1,011 CFPs (511 AD, 500 normal) from 707 subjects. Two foundation vision-language models were compared—Qwen3-VL-4B-Instruct (general-purpose) and medGemma-1.5-4b-it (medically adapted)—each in 1-, 3-, and 5-agent designs of increasing structure. The 3-agent design used a quality agent, a global lesion agent, and a judge; the 5-agent design added vascular density and vascular pattern agents. Crucially, in the 5-agent system the judge was not the final decision-maker: specialists produced structured observations, and the final label came from explicit aggregation rules rather than from a free-form response. Configurations were evaluated by accuracy, recall, specificity, precision, F1, inter-agent conflict, and runtime.

Results: Single-agent inference was strongly biased toward normal, with AD recall of just 0.0157 (Qwen) and 0.0020 (medGemma) despite high confidence; the 3-agent design improved this minimally (0.0372 and 0.0117). The 5-agent design produced the first substantial gain, raising recall to 0.3503 (Qwen) and 0.3425 (medGemma)—roughly twenty-fold—driven by the vascular specialists, implicating distributed vascular cues rather than focal lesions. Qwen was slightly more sensitive but noisier (specificity 0.6200; conflict 0.6034), whereas medGemma had the best overall balance (accuracy 0.5786, precision 0.6604, specificity 0.8200, F1 0.4510, conflict 0.2730) and ran faster. Notably, a single abnormal vascular density flag could override an otherwise reassuring judge to correctly recover an AD case.

Conclusions: Multi-agent decomposition can meaningfully improve retinal-based AI screening for subtle AD-associated abnormality over single-model inference. The key insight is that detection improved through structured division of labor among specialist agents rather than through a more powerful single model: adding dedicated vascular-density and vascular-pattern specialists raised the system's sensitivity to weak, distributed cues and recovered abnormal cases that direct single-model inference, or even the system's own final judge, would otherwise overlook. These preliminary single dataset results warrant validation in larger, external data; building on them, we plan to extend our prior RetinalGPT system into a collaborative multi-agent framework.

STUDENT POSTER # 207

SINGLE-NUCLEUS PROFILING REVEALS AGE-ASSOCIATED TRANSPOSABLE ELEMENT EXPRESSION ACROSS THE RHESUS MACAQUE BRAIN. Watkins K, Leinenweber K, Yang W, DeCasien AR, O'Neill MB, Bohlen MO, Melin AD, Higham JP, Montague MJ, Platt ML, Chiou KL, Shendure J, Snyder-Mackler N. Arizona State University; University of Washington; National Institute on Aging; University of Alabama at Birmingham; University of Pennsylvania; Howard Hughes Medical Institute; Seattle Hub For Synthetic Biology; Duke University; Allen Discovery Center For Cell Lineage Tracing; New York University; New York Consortium in Evolutionary Primatology; University of Oxford; University of Calgary; Arizona Alzheimer's Consortium.

Background: Aging is accompanied by a progressive loss of molecular fidelity and regulatory control across multiple levels of genome function. One consequence of this dysregulation is the increased expression of transposable elements (TEs), repetitive genomic sequences that are normally silenced but become more active with age. Because TE activation can compromise genomic stability and lead to inflammation, it has emerged as a potential contributor to age-related brain dysfunction and neurodegenerative disease. However, most evidence for age-associated TE activity comes from bulk tissue studies, limiting insight into cell-type-specific patterns.

Methods: Here, we leveraged a large-scale single-nucleus RNA-sequencing dataset from rhesus macaques, an established model for human brain aging. We used 5.3 million snRNAseq transcriptomes from 582 samples (11 regions; 55 animals; aged 0.4 to 21yr), which we resolved to 225 subtypes.

Results: Overall, TE expression (as a fraction of total transcripts) was significantly higher in older individuals in every brain region except the midbrain, where we observed lower TE expression in neurons and vascular cells (FDR < 0.05). We observed the biggest age-difference in TE expression in the hippocampus and entorhinal cortex regions (FDR < 0.05). Age-associated differences in TE expression were not uniform across TE classes, with the strongest signal observed in transcripts from short interspersed nuclear elements (SINEs) (FDR < 0.05). We next tested for cell subtype- and region-specific age effects on TE expression and found that 20% of TEs are differentially expressed with age in at least one context (FDR < 0.05), including 80% of tested DNA TEs, 21% of LINEs, 16% of SINEs, and 15% of LTRs. Age-associated differences in TE expression were most pronounced in both homeostatic and inflammatory microglial subtypes (mean beta_age=0.07, FDR < 0.05). We also identified higher expression of TEs in an ALS-associated oligodendrocyte subtype in the entorhinal cortex and thalamus of older animals (mean beta_age=0.08, FDR < 0.05). The largest numbers of individual age-differentially expressed TEs (aDE-TEs) were detected in astrocytes, which accounted for 28% of all aDE-TEs, and in the cerebellum, which accounted for 34% (FDR < 0.05).

Conclusions: Together, these findings reveal widespread, cell-type- and region-specific associations between age and TE expression in the primate brain. By characterizing TE expression dynamics at single-nucleus resolution, this work provides a framework for identifying cellular contexts in which TE activity may contribute to molecular vulnerability across the lifespan.

STUDENT POSTER # 208

RESTING-STATE FUNCTIONAL MAGNETIC RESONANCE IMAGING REVEALS DEFICITS IN MIDDLE CEREBRAL ARTERY (MCA) INTERHEMISPHERIC CONNECTIVITY IN EXTRACRANIAL CAROTID ARTERY DISEASE. Waughman X, Wiskoski H, Zahra S, French SR, Arias JC, Trouard TP, Alexander GE, Weinkauf CC. University of Arizona College of Medicine - Tucson; Arizona Alzheimer's Consortium.

Background: Extracranial carotid artery disease (ECAD) has been associated with increased risk of Alzheimer's Disease and Related Dementias (ADRD), but specific mechanisms are not clear. Because the internal carotid artery (ICA) primarily supplies the anterior cerebral artery (ACA) and middle cerebral artery (MCA) territories, these regions may be particularly vulnerable to downstream hemodynamic effects of carotid stenosis, which we planned to evaluate using resting-state functional magnetic resonance imaging (rs-fMRI).

Methods: The first 186 participants enrolled in the Carotids and Minds (CAM) study (50-85 years of age, ≥2 vascular risk factors and/or carotid artery stenosis) with completed imaging and stenosis grading were evaluated for these analyses. 20 participants with excessive motion (>20% of volumes with framewise displacement >0.5 mm) were excluded, resulting in 103 participants for analysis. rs-fMRI (gradient-echo EPI, TR/TE = 2000/30 ms; 2.5 mm isotropic, 300 volumes) was acquired on a 3T Siemens Skyra. fMRIprep and XCPD were used for anatomical image processing and denoising (36-parameter confound). Interhemispheric ACA-ACA, MCA-MCA, and PCA-PCA connectivity were calculated using the Johns Hopkins University (JHU) Arterial Territories atlas. Intrahemispheric MCA connectivity was derived from a composite of Automated Anatomical Labeling (AAL) regions with overlap with the JHU MCA territory.

Results: MCA-MCA interhemispheric connectivity significantly decreased with increasing stenosis severity ($r = -0.21$, $p < 0.05$). This association was strengthened after excluding subjects (n=19) with equivalent stenosis severity on both sides ($r = -0.39$, $p < 0.001$) and was independent of age, sex, history of stroke/TIA, cerebral small vessel disease severity, vascular risk factors, and framewise displacement. Additionally, mean intrahemispheric MCA connectivity differed across control, ipsilateral, and contralateral hemispheres (ANOVA $p = 0.04$). Importantly, the association between carotid stenosis severity and MCA-MCA interhemispheric connectivity remained significant after adjustment for ipsilateral intrahemispheric MCA connectivity ($r = -.39$, $p < 0.001$). No significant interhemispheric connectivity patterns were seen in the ACA-ACA ($r = -0.01$, $p = 0.955$) or PCA-PCA ($r = -0.00$, $p = 0.985$) vascular territories.

Conclusions: Carotid stenosis is associated with reductions in interhemispheric BOLD signaling, localizing to areas of the brain supplied by the carotid artery in the MCA territory. This suggests there may be functional brain differences associated with carotid stenosis. The relative contribution of vascular and neural mechanisms to this phenomenon remains to be determined.

STUDENT POSTER # 209

CORTICAL SURFACE AREA IS ASSOCIATED WITH MCI AND AD INDEPENDENT OF CORTICAL THICKNESS. Wiskoski HE, Zahra S, French SR, Arias JC, Alexander GE, Weinkauf CE. University of Arizona; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is associated with neurodegeneration and cortical atrophy that can be quantified using MRI-derived cortical thickness (cTH) or regional volume. However, cortical volume reflects two separate morphometric properties: cTH and cortical surface area (cSA). These two dimensions are highly heritable and have distinct genetic influences. cSA has been shown to be related to cognition and intelligence in development, but has been less explored in aging and dementia, yet may capture a distinct aspect of cortical vulnerability. In this study, we investigated whether cSA within AD-vulnerable brain regions is independently associated with dementia and mild cognitive impairment (MCI) diagnosis and future clinical progression.

Methods: Morphometric and clinical data were gathered from two large cohorts: the National Alzheimer's Coordinating Center (N=2,993) and the Alzheimer's Disease Neuroimaging Initiative (N=2,255). FreeSurfer-derived cSA, cTH, and volume were gathered from each cohort and values were summarized within an a priori AD-Signature composite. Cross-sectional analyses examined associations of cSA and cTH with clinical diagnosis including cognitively normal (NL), mild cognitive impairment (MCI), and AD and related dementias (ADRD). Models were adjusted for demographics, APOE e4 allele, and imaging characteristics. . Longitudinal analyses in ADNI (mean follow-up = 4 years, max = 15 years) assessed the association of baseline morphometrics with incident AD in participants who were NL or MCI at baseline.

Results: In NACC and ADNI, AD-Signature cSA and cTH were weakly correlated (r=0.02 and r=-0.04, respectively), and differed significantly across cognitive groups (both P<.001). Accounting for demographic, genetic, and imaging factors, and cTH as covariates, cSA was associated with increased odds of MCI and ADRD in both NACC (MCI: odds ratio [OR]=1.53; Dementia: OR=2.49; P<.001) and ADNI (MCI: OR=1.48; Dementia: OR=2.14; P<.001). In both cohorts, participants with both low cSA and low cTH (defined by lowest quartiles) showed the strongest cross-sectional association with MCI and ADRD, having greater odds than just low cTH or low volume. Baseline cSA was independently associated with incident AD after adjustment for cTH, and combined cSA/cTH models demonstrated better prognostic model fit than cTH alone (AIC=4059 vs 4076) or volume alone (AIC=4119).

Conclusions: These findings demonstrate that cSA contributes diagnostic and prognostic information about MCI and ADRD, independent from cTH in brain regions known to be most susceptible to ADRD. This suggests there may be significant value in considering both cTH and cSA when studying and clinically evaluating ADRD-related neurodegeneration.

STUDENT POSTER # 210

SGW-GAN: SLICED GROMOV-WASSERSTEIN GUIDED GANS FOR RETINAL FUNDUS IMAGE ENHANCEMENT WITH PRESERVED DISEASE-RELEVANT GEOMETRY. Xiong Y, Dong X, Zhu W, Li X, Dumitrascu O, Wang Y. Arizona State University; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Retinal fundus photography is a low-cost, non-invasive modality increasingly used to study neurovascular changes relevant to Alzheimer's disease and related dementias (ADRD), alongside its established role in screening for diabetic retinopathy (DR). However, real-world fundus images are frequently degraded by noise, uneven illumination, and artifacts, compromising both clinical interpretation and automated analysis. Existing GAN- and diffusion-based enhancement methods improve perceptual quality by aligning degraded images to a high-quality distribution, but our preliminary t-SNE analysis of RetFound-encoded features reveals that this distribution-matching objective can distort intra-class geometry: images of the same disease category become dispersed in feature space after enhancement, blurring previously well-separated class boundaries. This geometric distortion can harm downstream diagnostic tasks even when conventional metrics (PSNR, SSIM) appear favorable. We hypothesized that explicitly preserving internal relational geometry during enhancement would yield images that are both visually improved and more clinically reliable.

Methods: We propose SGW-GAN, the first framework incorporating Sliced Gromov-Wasserstein (SGW) discrepancy into retinal image enhancement. The Gromov-Wasserstein (GW) distance compares distributions through internal pairwise distances rather than point correspondence, naturally preserving intra-class structure, but its cubic cost is prohibitive for high-resolution images. SGW approximates GW via random one-dimensional projections, reducing cost by orders of magnitude while retaining relational fidelity. Our generator (U-Net with channel/spatial attention) is trained under a WGAN-GP objective combining: (1) RMSE reconstruction loss preventing over-enhancement, (2) SGW loss on frozen RetFound encoder embeddings enforcing relational consistency, and (3) adversarial loss for visual realism. We trained and evaluated on the EyeQ dataset (224×224) with 256 SGW projections for 200 epochs. Evaluation combined image-quality metrics (PSNR, SSIM, FID), downstream DR grading via an NN-MobileNet classifier (accuracy, F1, AUC), and full GW discrepancy as a direct measure of geometric preservation.

Results: Compared against six baselines (CycleGAN, WGAN, OTTGAN, OTEGAN, Context-Aware OT, CUNSB-RFIE), SGW-GAN achieved the best FID (18.14 vs. 23.78–74.89) and the best downstream DR grading performance (accuracy 0.7814, F1 0.7749, AUC 0.9297), despite modestly lower SSIM/PSNR than top perceptual baselines. SGW-GAN also achieved the lowest GW discrepancy (599.92 vs. next-best 794.95), confirming superior preservation of intra-class geometry. Ablation showed that removing the SGW term sharply increased GW discrepancy (847.68), confirming it as the key driver of geometry preservation, while removing RMSE degraded structural fidelity of eyeball boundaries. Qualitative results showed SGW-GAN better preserved fine vascular structures and avoided artificial homogenization across disease severities seen in baseline methods.

Conclusions: SGW-GAN demonstrates that explicitly preserving intra-class relational geometry via efficient SGW regularization yields enhanced retinal images more diagnostically reliable than those from methods optimized purely for perceptual quality. This finding suggests PSNR/SSIM are insufficient proxies for clinical utility and that relational-structure preservation should be prioritized in medical image enhancement. As retinal vasculature is increasingly studied as a non-invasive biomarker for cerebrovascular and neurodegenerative changes associated with ADRD, enhancement methods preserving disease-relevant structure may be particularly valuable for downstream retinal biomarker extraction in dementia research.

STUDENT POSTER # 211

CEREBELLAR SYNAPTIC DYSFUNCTION AND STRUCTURAL PLASTICITY IN ALZHEIMER'S DISEASE. Yerramilli A, Hashim A, Mufson EJ, Perez SE, Verpeut JL. Arizona State University; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is characterized by progressive cognitive decline associated with synaptic dysfunction and neurodegeneration. Although AD pathology has been extensively studied in cortical and hippocampal regions, the cerebellum remains relatively understudied despite growing evidence supporting its role in cognitive function. Previous work from our laboratory using postmortem cerebellar tissue from participants in the Rush Religious Orders Study (RROS) with premortem clinical diagnoses of no cognitive impairment (NCI), mild cognitive impairment (MCI), and Alzheimer's disease (AD) revealed compromised myelin integrity in the cerebellum of AD patients. Specifically, myelin basic protein (MBP) intensity was significantly reduced in the cerebellar white matter and granule cell layer of AD cases and was associated with cognitive impairment and increased AD neuropathological burden. These findings indicate a selective vulnerability of the cerebellum in AD and provide the rationale for the current investigation examining synaptic integrity and neuronal structural plasticity during AD progression.

Methods: Formalin-fixed, paraffin-embedded cerebellar sections from NCI, MCI, and AD cases were immunostained for the presynaptic markers synaptophysin and α-synuclein, the dendritic spine-associated protein drebrin, and the structural neuronal marker microtubule-associated protein 2 (MAP2). Whole-slide images were acquired using a brightfield scanner and analyzed with QuPath software. Quantitative and qualitative analyses were performed to assess changes in protein expression across cerebellar layers and disease stages. These analyses were designed to determine whether markers of dendritic spine plasticity and neuronal structure precede changes in presynaptic markers during the transition from normal cognition to MCI and AD.

Results: Previous analyses revealed significantly reduced MBP optical intensity in the cerebellar white matter (AD vs. NCI, $p = 0.0232$) and granule cell layer (AD vs. NCI, $p = 0.0015$; AD vs. MCI, $p = 0.0028$) of AD cases. In the granule cell layer, MBP intensity was positively associated with global cognitive scores, episodic memory, visuospatial performance, and Mini-Mental State Examination (MMSE) scores. MBP intensity was also negatively associated with Braak stage and amyloid plaque burden. These findings indicate compromised cerebellar myelin integrity in AD and support the investigation of synaptic and structural markers during disease progression.

Conclusions: The observed reductions in cerebellar MBP expression support a selective vulnerability of the cerebellum in AD and suggest that cerebellar pathology is associated with cognitive decline and disease severity. Ongoing analyses of synaptic and structural markers will further define the relationship between cerebellar neuronal integrity and AD progression. Together, these studies extend our previous findings and may provide new insights into the contribution of cerebellar dysfunction to the pathogenesis of AD.

STUDENT POSTER # 212

SEMANTIC TRAJECTORY METRICS FROM VERBAL FLUENCY: A POTENTIAL APPROACH TO CHARACTERIZING SEMANTIC SEARCH IN COGNITIVE IMPAIRMENT. Zhang H, Chou Y-h. University of Arizona; Arizona Alzheimer's Consortium.

Background: Verbal fluency is a widely used neuropsychological test sensitive to aging and cognitive decline, traditionally tied to executive and language systems. Beyond total word count, the sequence in which words are produced may reveal how a person navigates semantic memory, potentially providing a behavioral marker of conceptual navigation supported by entorhinal-hippocampal circuitry, an early target of Alzheimer's disease pathology. As an initial step toward the goal, we developed an automated pipeline to derive semantic trajectory metrics from verbal fluency performance and evaluated their construct validity and reliability.

Methods: We analyzed verbal fluency data from the DementiaBank Pitt Corpus (animals, foods, F, and S fluency; 158 participants, 431 word lists; predominantly MCI-to-AD). After rule-based extraction with manual quality control, words were embedded in a semantic space using fastText (300-dimensional word vectors). For each list, we computed conventional word count and three embedding-based measures: semantic spread (content breadth), mean step similarity (local semantic continuity), and a model-derived semantic-foraging parameter (b_sem) reflecting transitions between semantic clusters. Permutation analyses compared observed word sequences with randomly shuffled sequences to quantify order-specific structure. We assessed construct validity (category vs. letter) and reliability (split-half, task-pooling, cross-task consistency).

Results: Construct validity. Category fluency tasks produced significantly more coherent semantic trajectories than letter fluency tasks, supporting construct validity. Word-generation order contained meaningful semantic structure beyond chance, particularly in category fluency. The semantic foraging parameter (b_sem) demonstrated the same category-specific pattern and was independent of total word count (r = 0.00).

Reliability. Split-half reliability was acceptable for mean step similarity (0.68) and modest for b_sem (0.43), rising to 0.62 for b_sem when the category tasks (animals + foods) were aggregated. Trajectory metrics showed significant consistency across category fluency tasks (animals and foods) but not between category and letter fluency tasks, indicating that they capture semantic search processes specific to category-based retrieval.
Exploratory clinical validity. Semantic spread provided incremental prediction of MMSE performance beyond demographics and word count in the MCI/possible Alzheimer's disease subgroup (R-squared = +0.092, p = 0.011, N = 25).

Conclusions: We developed a reproducible pipeline to derive trajectory metrics from word lists and validated their construct validity and reliability. The trajectory metrics capture a genuine, word-count-independent property of semantic search specific to category tasks. Although b_sem is promising as a trajectory index, its trait-level reliability is limited by the number of produced words. Future studies, therefore, require longer responses (merged tasks, narrative speech, or free association). We further plan to extend the framework to at-risk, cognitively unimpaired older adults using detailed neuropsychological batteries and neuroimaging to test whether semantic-trajectory geometry indexes early entorhinal-hippocampal dysfunction.

STUDENT POSTER # 213

PODCARING: INVESTIGATING THE FEASIBILITY AND EFFICACY OF THE DEMENTIA UNTANGLED PODCAST FOR CAREGIVERS AND PERSONS WITH EARLY-STAGE COGNITIVE IMPAIRMENT. Zhang J, Mulder H, High N, Bauer R, Knox J, Chen Y, Nisson L, Langbaum JB, Ayers A, Huentelman M, Coon D, Pruzin J. University of Arizona College of Medicine - Phoenix; Banner Alzheimer's Institute; Banner Alzheimer's Institute - Tucson; Translational Genomics Research Institute; Arizona State University Edson College of Nursing And Health Innovation; Arizona Alzheimer's Consortium.

Background: Caregivers of persons with neurodegenerative disease face substantial stress and burden that can adversely affect their health and the well-being of the person they care for. People living with cognitive impairment experience stigmatization that may lead to depression and hopelessness. Dementia Untangled is a podcast offering expert guidance and support in a conversational format. This prospective, online study evaluated the feasibility of Dementia Untangled as a structured intervention for caregivers and persons with early-stage cognitive impairment and explored effects on burden, mood and quality of life.

Methods: We recruited caregivers and persons with early-stage cognitive impairment (MCI/mild dementia from any cause) through newsletters/distribution lists and at dementia focused clinics/programs. Both groups completed pre-listening surveys, listened to 8 (caregivers) or 4 (MCI/mild dementia) episodes curated separately for each group, then completed post-listening surveys. Caregivers completed the following scales before and after listening to episodes: Problem Solving Self-Efficacy (PSSE), UCLA 3-item Loneliness, Center of Epidemiological Studies-Depression (CES-D), Zarit Caregiver Burden Assessment (12 item), and Hopkins Symptom Checklist (Anger Subscale). Persons with MCI/mild dementia completed the Mood Scale, Self-Esteem Subscale, UCLA 3-item Loneliness, Quality of Life-Alzheimer's Disease (QOL-AD), and CES-D. We compared pre- and post-listening outcome measures using dependent t-tests with Bonferroni correction for multiple comparisons.

Results: Caregivers had a mean age of 61.8 years and persons with cognitive impairment had a mean age of 73.3 years. Over 5 months, 247 caregivers enrolled; 117 (47.4%) completed the study. Over 7 months, 33 persons with MCI/mild dementia enrolled; 20 (60.6%) completed the study. Both groups reported a positive experience (3-point Likert: 2.48 and 2.55). Exploratory pre-post analyses in caregivers who completed the study showed modest, statistically significant improvements (all $p < 0.001$) on the CES-D ($12.31 \pm 6.49 \rightarrow 10.30 \pm 6.03$), Zarit Burden Short Form ($23.79 \pm 7.73 \rightarrow 21.52 \pm 7.73$), Hopkins Symptom Checklist Anger Subscale ($7.84 \pm 3.68 \rightarrow 6.51 \pm 3.42$), and two of four Problem Solving Self-Efficacy domains. Results remained significant when including all participants who began the study. Change on the UCLA 3-Item Loneliness Scale was in the expected direction but did not meet the corrected significance threshold ($6.04 \pm 1.88 \rightarrow 5.71 \pm 1.89$, $p = 0.012$). Changes in persons with MCI/dementia did not reach significance in this underpowered feasibility study.

Conclusions: The Dementia Untangled podcast is a feasible, structured intervention for caregivers and persons with early-stage cognitive impairment. Among caregivers, preliminary results suggest reduced burden, depression, and anger, warranting a larger controlled efficacy trial.

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Additional Abstracts

EFFICIENT BRAIN PENETRATING PRODRUGS FOR THE TREATMENT OF ALZHEIMER'S DISEASE. Brodsky S, Olsen M. Midwestern University; Arizona Alzheimer's Consortium.

Background: Alzheimer's Disease (AD) is a progressive neurodegenerative disease associated with mitochondrial dysfunction and neuronal death. Butenedioic esters (BDE) are FDA approved drugs with demonstrated mitochondrial biogenesis triggering activity that are currently being studied in preclinical and clinical trials. However, while BDE metabolites can penetrate the Central Nervous System (CNS), the dose that reaches the brain is only about 12%, while the remaining 88% is either rapidly metabolized or results in peripheral side effects. These side effects limit the dose and beneficial activity of BDEs. This project designed a series of BDEs to specifically target the CNS for efficient uptake.

Methods: Molecules were designed using StarDrop by Optibrium. Selected compounds were synthesized and characterized. Compounds were further evaluated for chemical and biochemical stability. A select number of compounds were evaluated for brain penetration and biodistribution.

Results: Some compounds could not be readily synthesized. Among the compounds that could be synthesized, the purity of some compounds as less than optimal, but sufficient for preliminary evaluation. Some compounds were prepared at very high purity and yield. Chemical and biochemical stability had a wide distribution, but one compound had particularly impressive stability. This compound was evaluated in mouse pharmacokinetic models and was found to be extraordinarily effective at releasing the desired active drug substance (ADS) in the brain relative to the peripheral tissue.

Conclusions: Prodrug designs for butenedioic acids can be very successful in CNS drug delivery. Triggering neuronal mitochondrial biogenesis has the potential to be a disease modifying therapy for AD using a completely different method and approach from beta-amyloid or Tau approaches.

HYPERTENSION, METABOLIC DYSREGULATION, AND ALZHEIMER'S DISEASE: A VASCULAR–METABOLIC MODEL OF BRAIN AGING. Bryant N. Midwestern University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease reflects a complex interaction of amyloid and tau pathology, vascular damage, and metabolic abnormalities. Nearly 45% of global dementia cases involve modifiable risk factors, many of which are cardiovascular. Chronic hypertension damages cerebral blood vessels, producing arterial stiffness, endothelial dysfunction, and blood-brain barrier disruption that reduce cerebral perfusion and limit clearance of neurotoxic proteins. Metabolic abnormalities, including insulin resistance, cerebral glucose hypometabolism, and mitochondrial failure, emerge decades before symptoms appear. Peripheral insulin resistance predicts brain amyloid deposition, and metabolic syndrome raises the risk of all-cause and vascular dementia. This review synthesizes recent literature on hypertension, metabolic dysfunction, and Alzheimer's disease to describe how these variables interact and to identify opportunities for early intervention.

Methods: A focused narrative review examined peer-reviewed literature from 2021 to 2026 in PubMed, Embase, and the Cochrane Library, using terms related to hypertension, cerebral blood flow, blood-brain barrier integrity, insulin resistance, brain hypometabolism, and cognitive decline. Priority was given to systematic reviews, meta-analyses, and large epidemiological studies, including the SPRINT-MIND trial and its follow-up analyses. Evidence on pericyte degeneration, amyloid clearance, brain insulin signaling, FDG-PET glucose hypometabolism, and mitochondrial bioenergetics was reviewed alongside observational data on GLP-1 receptor agonists, SGLT2 inhibitors, and current clinical guidelines.

Results: Hypertension contributes to cognitive decline through overlapping pathways. Elevated blood pressure produces cerebral small vessel disease and blood-brain barrier damage that impair amyloid-beta clearance. Cerebral hypoperfusion appears during early Braak tangle stages, and endothelin-1 and VEGF-A levels correlate with perfusion and phosphorylated tau. In SPRINT-MIND, intensive blood pressure control (systolic target below 120 mmHg) reduced combined risk of mild cognitive impairment or probable dementia (HR 0.89, 95% CI 0.79-0.99) over seven years, and a meta-analysis of five placebo-controlled trials found antihypertensive therapy lowered incident dementia risk (OR 0.87, 95% CI 0.75-0.99). Metabolic dysfunction acts independently: peripheral insulin resistance predicts amyloid accumulation years before symptoms, mitochondrial failure accelerates tau pathology, and FDG-PET detects glucose hypometabolism in asymptomatic at-risk adults. Midlife hypertension and diabetes together raise dementia risk beyond their individual effects, and metabolic syndrome correlates with smaller brain and hippocampal volumes. In type 2 diabetes, GLP-1 receptor agonists and SGLT2 inhibitors correlate with 33% and 43% lower Alzheimer's disease risk, respectively, compared with other glucose-lowering drugs.

Conclusions: These findings support a vascular-metabolic model in which hypertension and metabolic dysfunction converge to accelerate neurodegeneration, positioning cardiometabolic health alongside amyloid pathology as a central determinant of brain resilience. Midlife hypertension is associated with a 40 to 60 percent increase in late-life dementia risk, and controlling blood pressure to 130/80 mmHg is recommended by cardiovascular guidelines to help prevent cognitive impairment. Addressing modifiable risk factors could theoretically prevent nearly half of global dementia cases. GLP-1 receptor agonists may offer neuroprotection through improved insulin signaling, reduced neuroinflammation, and better cerebral blood flow. Early management of hypertension, insulin resistance, and obesity offers a practical public health strategy to reduce Alzheimer's disease burden, and future trials should test multimodal cardiometabolic interventions and track cognitive outcomes over time.

STRESS AND SEX EFFECTS ON RELAXIN-3 EXPRESSION IN THE AGING NUCLEUS INCERTUS. Fermaint M, De Louise M, Tadesse S, Ramos J, Trigueros J, Contreras J, Chakraborti A, Gundlach A, De Ávila C. University of Arizona College of Medicine - Phoenix; The Florey Institute of Neuroscience and Mental Health; The University of Melbourne; Arizona Alzheimer's Consortium.

Background: Stress-related neuropsychiatric symptoms, including anxiety, are common in aging and frequently precede cognitive decline associated with neurodegenerative disorders. Dysregulation of stress-responsive neural circuits is therefore considered a key feature of vulnerability during aging. The brainstem contains several nuclei that integrate autonomic, affective, and cognitive functions and show early alterations in aging and Alzheimer's disease. Among these, the nucleus incertus (NI) is a highly stress-responsive pontine nucleus that modulates arousal, anxiety-like behavior, and memory through widespread projections to limbic and hippocampal circuits. The NI is the primary source of the neuropeptide relaxin-3 (RLN3), which signals through the inhibitory G-protein–coupled receptor RXFP3, prominently expressed by hippocampal somatostatin interneurons—cell populations known to be vulnerable during aging and neurodegeneration. Preclinical studies demonstrate that NI neurons, including RLN3-expressing cells, are robustly activated by acute stress; however, how stress and aging interact to influence RLN3 expression in midlife animals, and whether these effects differ by sex, remains insufficiently characterized.

Methods: Wild-type C57BL/6J male (n=8) and female (n=10) mice aged 12 months were subjected to an acute restraint stress paradigm (1 hour) or maintained as unstressed controls. Animals were sacrificed immediately following stress exposure. Brains were perfused with phosphate-buffered saline and fixed with 4% paraformaldehyde, followed by post-fixation and cryoprotection in paraformaldehyde/sucrose solutions. Brains were frozen and stored at −80 °C until cryosectioning. Six, fifteen-micron, coronal brainstem sections per animal encompassing the NI were processed for multiplex RNAscope in situ hybridization to detect RLN3 mRNA. Images were acquired, and the signal quantified using ImageJ software. Statistical analysis of the results employed a t-test or analysis of variance (ANOVA) to determine significant differences in mRNA levels between different groups.

Results: We expect acute stress exposure to be associated with increased RLN3 mRNA expression in the NI relative to unstressed controls. Sex-specific differences are anticipated, with a greater stress-associated increase in RLN3 mRNA levels in females compared to males. In addition, based on prior reports in young adult rodents, we expect overall RLN3 mRNA expression in 12-month-old mice to be lower than levels described in younger animals, consistent with age-related alterations in NI peptidergic signaling. These findings are expected to provide insight into how stress, sex, and aging intersect to shape RLN3 expression in a key brainstem nucleus involved in anxiety and cognitive regulation.

Conclusions: This initial study will reveal stress- and sex-associated patterns of RLN3 mRNA expression in the aging NI. By focusing on a midlife time point, the results are expected to inform models of how age-related changes in the NI may contribute to vulnerability in cognitive and affective domains, providing a foundation for future mechanistic and translational studies of the RLN3/RXFP3 system.

QUANTIFICATION OF RELAXIN-3-IMMUNOREACTIVITY LEVELS IN THE HUMAN NUCLEUS INCERTUS IN AGING AND ALZHEIMER'S DISEASE. Fuentes S, De Louise M, Fermaint M, Intorcia A, Serrano GE, Beach TG, Gundlach A, De Ávila C. University of Arizona College of Medicine - Phoenix; The University of Melbourne; Arizona Alzheimer's Consortium.

Background: Background: Brainstem nuclei involved in arousal, stress integration, and state-dependent modulation are increasingly recognized as altered in aging and neurodegenerative disease. The nucleus incertus (NI) is a small GABAergic structure in the pontine tegmentum that exerts widespread modulatory influence over forebrain circuits through its principal neuropeptide, relaxin-3 (RLN3). This system regulates behavioral state and stress responsiveness via projections to hippocampal and septohippocampal networks. Alterations in these functions are prominent features of Alzheimer's disease (AD), yet human neuropathological studies of the NI remain scarce. This gap reflects both the anatomical complexity of the brainstem and the limited use of molecular markers capable of reliably delineating small nuclei in postmortem tissue. Quantifying RLN3 protein levels in the human NI across aging and AD provides an opportunity to assess disease-associated changes in a stress- and arousal-related brainstem system that has not been systematically examined in humans.

Methods: Methods: Formalin-fixed, paraffin-embedded pons tissue was obtained from the Brain and Body Donation Program (Sun City, AZ, USA). Six-micron serial sections spanning the pons from anterior to posterior were collected from individuals aged 65 years or older diagnosed with AD and from non-demented controls (12 IDs per group). Cases and controls were matched for age, sex, postmortem interval, and ApoE status. Immunohistochemistry was performed using a validated RLN3 antibody to delineate the NI and quantify protein levels, while phosphorylated tau was assessed on adjacent sections using the AT8 antibody. Bright-field microscopy was used for image acquisition, and quantitative analysis of immunosignal intensity and area was conducted using QuPath software. Statistical comparisons between groups were performed using ANOVA.

Results: Expected Outcomes: This study is expected to establish robust anatomical delineation of the human NI using RLN3 as a molecular reference and to quantify RLN3 protein levels in aging and AD. Group differences in RLN3 immunoreactivity may indicate disease-associated alterations in this brainstem neuropeptide system.

Conclusions: Conclusion: This work provides a quantitative neuropathological assessment of RLN3 expression in the human NI using well-matched postmortem tissue. By defining nucleus boundaries and measuring RLN3 protein levels in aging and AD, this study contributes foundational data on a stress- and arousal-related brainstem systems that may be relevant to disease mechanisms and biomarker development.

INTEGRATED PROTEOMIC AND PHOSPHOPROTEOMIC PROFILING REVEALS DIVERGENT PATTERNS OF SYNAPTIC VULNERABILITY ACROSS ALS, FTLD, AND ALZHEIMER'S DISEASE. Gopalakrishnan L, Kaushik L, Bakkar N, Medina DX, Sharma R, Martinez MN, Hansen NP, Pirrotte P, Bowser R. Barrow Neurological Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Synaptic dysfunction is an early and convergent feature of neurodegenerative diseases, although the molecular mechanisms underlying synaptic vulnerability may differ across amyotrophic lateral sclerosis (ALS), frontotemporal lobar degeneration (FTLD), and Alzheimer's disease (AD). ALS and FTLD exist along a clinical and pathological spectrum, while AD shares several downstream processes, including altered protein homeostasis, mitochondrial dysfunction, neuroinflammation, and synaptic loss. Comparative analysis of the synaptic proteome and phosphoproteome may therefore identify both shared and disease-specific mechanisms of neurodegeneration.

Methods: Synaptosome-enriched fractions were isolated from postmortem frontal cortex tissue from individuals with ALS, FTLD, AD, and neurologically normal controls (n=4 per group). Global proteomic and phosphoproteomic profiling was performed using tandem mass tag-based quantitative mass spectrometry. Protein and phosphosite abundances were log2-transformed and normalized prior to linear modeling with pairwise contrasts, including ALS versus control, FTLD versus control, AD versus control, and disease-to-disease comparisons. Nominal and Benjamini–Hochberg-adjusted p values with log2 fold changes were used to identify disease-associated alterations. Phosphosite changes were interpreted alongside corresponding total protein abundance to distinguish phosphorylation-specific regulation from changes driven by protein expression. Pathway enrichment, protein-network analysis, and kinase activity inference were then used to define shared and disease-specific alterations.

Results: Comparative profiling identified divergent patterns of synaptic proteome and phosphoproteome remodeling across ALS, FTLD, and AD. Across the global synaptosome proteome, 8,212 proteins were identified, of which 875 showed significant differential expression across disease groups. ALS was characterized by altered mitochondrial function, calcium handling, local translational control, cytoskeletal regulation and PKA-, PKC-, and MNK-related signaling. Representative phosphorylation changes involved CACNA1A, ATP2B2, MFN2, NDUFS2, EIF4E, and PPP1R12A. In contrast, FTLD showed more prominent MAPK-, CDK-, and GSK3-associated phosphorylation, consistent with disruption of cytoskeletal organization, intracellular transport, adhesion, and synaptic structural maintenance. AD showed a more heterogeneous frontal-cortex synaptic signature, with alterations in vesicle trafficking, cytoskeletal organization, and RNA-regulatory pathways. Many disease-associated alterations were detected primarily at the phosphosite level without corresponding changes in total protein abundance. Shared alterations involved synaptic signaling, metabolism, vesicle trafficking, cytoskeletal remodeling, and protein homeostasis, although the regulatory context differed across diseases.

Conclusions: Integrated synaptosomal proteomic and phosphoproteomic profiling revealed disease-specific molecular programs of synaptic vulnerability across ALS, FTLD, and AD. Together, these results indicate that disease-associated synaptic dysfunction may reflect changes in the regulation of existing synaptic proteins, rather than broad changes in total protein abundance. These findings highlight distinct regulatory mechanisms across neurodegenerative diseases and identify synaptic signaling pathways with mechanistic and therapeutic relevance.

REGIONAL AND DEMOGRAPHICS DIFFERENCE IN THE IMPACT OF HIGH AMBIENT TEMPERATURE EXPOSURE ON ALZHEIMER'S DISEASE AND RELATED DEMENTIAS HOSPITALIZATION IN MEDICARE BENEFICIARIES. Karway G, Killion J, Krzyzanowski B, Racette B. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease and related dementias (ADRD) affects 6.9 million adults aged 65 and older in the US and is projected to reach 13.8 million by 2060. As prevalence rises, ADRD-related hospitalizations and health care costs will increase. Extreme temperatures may exacerbate ADRD by impairing thermoregulation, disrupting neurological homeostasis, and increasing oxidative stress. The impact of extreme temperatures on ADRD hospitalizations in the US is understudied. The aim of this study was to investigate the regional impact of local heat stress on Alzheimer's disease and related dementias (ADRD).

Methods: Using a time-stratified case-crossover design, we identified beneficiaries in 2018 Medicare claims data who were hospitalized due to ADRD, defined as an ICD-10 diagnosis code in the first 10 positions on the claim, from April-October. We classified the case day as the ADRD admission date and controls days were matched on the same year, month, and day of the week. We used the latitude and longitude of the beneficiaries' residential zip+4 to link the 2018 average daily temperature obtained from the National Oceanic and Atmospheric Administration. Temperature exposure was classified using location-specific percentiles, with the 50th percentile representing typical temperatures. We used a distributed lag nonlinear model within conditional logistic regression framework to assess the association between temperature and ADRD hospitalizations.

Results: Our analysis in 2018 identified 163,128 unique beneficiaries within the United States during the warmer months. We found that exposure to extreme heat (defined as the 99th vs. 50th percentile of temperature) was significantly associated with elevated odds of ADRD hospitalization on the day of exposure (2.41, 95% CI: 1.05-5.43), and at 3- and 6-day lags ((1.19, 95% CI: 1.12-1.27 and 1.22, 95% CI: 1.14-1.31). The impact of heat demonstrated heterogeneity across demographic groups, with more pronounced estimated effects in females, White beneficiaries, older individuals, and those dually eligible for Medicare. Examining the nine US divisions, heat effects on ADRD admissions varied according to the lag period, with the greatest estimated hospitalization risks appearing in the East North Central, Pacific, and West North Central divisions. Similarly, heat impacts on ADRD also displayed state-level variation across the United States.

Conclusions: Clinicians should recognize extreme heat as a risk for ADRD patients, especially among females, older adults, and white beneficiaries. Tailored interventions, including hydration, cooling, and medication review, are essential to reduce hospitalization risks, particularly in high-risk states and regions.

NEUTROPHIL ACTIVATION IN CHOROID PLEXUS OF AMYOTROPHIC LATERAL SCLEROSIS. Kwapiszeski H, Thomas J, Gopalakrishna L, Bowser R, Bakkar N. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by progressive loss of upper and lower motor neurons. ALS is a heterogenous disease with 90 percent sporadic occurrence and 10 percent genetic, with C9orf72 (C9) hexanucleotide repeat expansion as the most predominant mutation. The range of age, onset locations, disease durations, and progression, all make diagnosis, patient stratification, and treatment challenging. ALS molecular mechanisms span from protein aggregation and excitotoxicity to neuroinflammation. The choroid plexus (CP), a highly vascularized tissue in the brain's ventricles, secretes cerebrospinal fluid (CSF), acts as the blood CSF barrier, and plays a critical role in regulating immune trafficking between the periphery and central nervous systems. CP dysregulation, including increased volume and extracellular matrix alterations, has been shown across neurodegenerative diseases such as ALS, frontotemporal dementia (FTD), and Alzheimer's Disease. Previously, in postmortem tissue from CP of ALS subjects, our lab identified loss of tight junctions and endothelial cell damage, along with increased immune infiltration and platelet activation.

Methods: We performed DIA-based proteomics on human postmortem CP tissue from ALS (n=18), ALS-FTD (n=15), and non-neurological disease control (NNDC, n=7) subjects. Protein identification and differential expression analysis (DEA) was performed to identify significantly altered proteins with a 2-fold change. Functional annotation was implemented to gain insight into pathways that are dysregulated in disease. The proteomics data was validated by investigating neutrophil counts in CP human postmortem tissue through immunohistochemistry.

Results: Proteomics results identify 7682 proteins and DEA highlight distinct differences in CP protein signatures across ALS and ALS-FTD, even though these two are on a disease continuum. ALS compared to both ALS-FTD and NNDC demonstrates a significant increase in immune proteins, specifically neutrophil and platelet associated proteins, such as NE, MPO, and GP1BA. Functional annotation highlights neutrophil activation as enriched in ALS. Immunohistochemistry demonstrates increased NE positive neutrophils in sporadic ALS compared to C9ALS, FTD, and NNDC. ALS subjects with faster disease duration (≤24 months) showed a significant increase in neutrophils compared to slower disease duration subjects (≥47 months). Most neutrophils remain in the vasculature of CP tissue, although occasionally stromal neutrophils or NET structures are observed.

Conclusions: Our study identifies innate immune activation as a distinct CP proteomic signature in ALS. We highlight neutrophil and platelet activation to be key differentiating factors between ALS and ALS-FTD. Our study also reports increased expression of neutrophil activation markers in CP vasculature, especially in subjects with faster disease duration. Neutrophil activation may contribute to CP breakdown and systemic inflammation in ALS, which correlates with worse disease outcomes. Together, this data suggests that neutrophil activation is a key dysregulated pathway that will be useful to develop patient stratification or prognostic biomarkers, as well as provide a mechanistic target for ALS.

IDISCO VALIDATION IN HUMAN CORTEX AND 3D MAPPING OF THE NUCLEUS INCERTUS IN ALZHEIMER'S DISEASE. Macias K, Fermaint M, De Louise M, Intorcia A, Serrano GE, Beach TG, Gundlach A, De Ávila C. University of Arizona College of Medicine - Phoenix; Banner Sun Health Research Institute; The University of Melbourne; Arizona Alzheimer's Consortium.

Background: The nucleus incertus (NI) is a small GABAergic brainstem nucleus positioned in the pontine tegmentum that serves as a critical modulatory hub for arousal, stress responsiveness, and memory-related circuitry. NI neurons are the primary central source of the neuropeptide relaxin-3 (RLN3), which signals through its cognate receptor RXFP3 to influence hippocampal and septohippocampal networks implicated in contextual memory, anxiety, and behavioral state regulation. Preclinical studies demonstrate that NI/RLN3 signaling modulates hippocampal somatostatin interneurons—cell populations known to be vulnerable in aging and Alzheimer's disease (AD). Despite growing evidence that brainstem nuclei exhibit early AD-related tau pathology, the NI has not been systematically examined in the human brain, in part due to its small size and deep anatomical location. Traditional two-dimensional histological approaches limit accurate assessment of its cytoarchitecture and pathological burden. Three-dimensional (3D) tissue-clearing approaches, such as iDISCO, offer a powerful strategy to visualize intact cellular and molecular organization in postmortem human tissue. In this study, RLN3 will be used to identify NI neurons, corticotropin-releasing hormone receptor 1 (CRHR1) will be examined as a marker of stress-related signaling, and AT8 will be used to detect phosphorylated tau pathology associated with AD, enabling integrated analysis of neuronal identity, stress responsiveness, and neurodegenerative pathology within the human NI.

Methods: Fresh postmortem human cortical tissue (N equal 6) from the Banner Brain and Body Donation Program (Sun City, AZ, USA) will be used to adapt and validate an iDISCO-based tissue-clearing and immunolabeling protocol optimized for aged, non-perfused tissue. Brain tissue will be collected during autopsies and placed in a medium solution before the start of the iDISCO protocol. Tissue blocks will undergo fixation, permeabilization, blocking, and immunolabeling using antibodies including RLN3, CRHR1, and AT8. Samples will then be subjected to methanol-based dehydration, dichloromethane delipidation, and dibenzyl ether clearing to achieve optical transparency. Cleared tissues will be imaged using light-sheet microscopy to generate high-resolution 3D reconstructions of the cortical areas. Following validation, the protocol will be applied to NI samples from individuals with AD and non-demented controls. Quantitative spatial analyses, such as nearest neighbor analysis and total immunosignal volume and cell count, will be performed to compare marker expression and distribution between AD and controls.
Expected Outcomes: This study is expected to successfully adapt and validate a 3D tissue-clearing and immunolabeling protocol for human postmortem brain tissue and to generate detailed 3D reconstructions of the NI. RLN3 labeling is expected to delineate the cytoarchitectural organization and neuronal distribution of the human NI, while CRHR1 expression will provide insight into the engagement of NI neurons in stress-responsive signaling pathways. AT8 immunolabeling will be used to assess the presence and spatial relationship of AD-related tau pathology within or adjacent to NI neurons. Comparative analyses are expected to uncover disease-associated alterations in the NI structure and molecular signatures associated with AD neurodegeneration.

Conclusion: This study employs an adapted iDISCO tissue-clearing and immunolabeling approach to investigate the human NI in three dimensions. By integrating markers of neuronal identity (RLN3), stress signaling (CRHR1), and AD pathology (AT8), this work aims to advance understanding of how stress-responsive brainstem circuits are organized in the human brain and how they may be altered in AD. These findings will establish a foundational framework for future 3D studies and contribute to a broader understanding of non-cortical circuits relevant to cognitive decline and neurodegeneration.

OLDER ADULTS' EXECUTIVE FUNCTION REFLECTED IN FREE-RESPONSE SPOKEN LANGUAGE TASK. Pfeifer VA, Ryan L, Levin, B, PAN Consortium, Mehl MR. University of Missouri - Kansas City; University of Arizona; University of Miami; Precision Aging Network; Arizona Alzheimer's Consortium.

Background: A key ingredient to successful aging is maintaining good executive functioning (EF), essential top-down cognitive processes that are effortful to use and sustain, such as inhibition, working memory, and cognitive flexibility. EF and cognition have traditionally been assessed using standardized neuropsychological testing, where performance may be impacted by practice effects and participant motivation and mood. An emerging line of research has tested if language markers in participant speech relate to EF [1] and might be used to develop novel assessments. The present study tested whether a standardized free-recall speech task can predict EF.
[1] https://doi.org/10.1093/geronb/gbaa055

Methods: Participants (N = 1,140, Mage = 64.28, SD = 7.94) were selected from the Precision Aging Network dataset. Participants had to have a valid transcript available for the Episodic Memory Speech Task, and had to have completed at least one of five tasks: Flanker (FLK, n = 871 inhibition), Keep Track (KT, n = 886, working memory), Letter Number (LN, n = 574; cognitive flexibility), Simple and Choice Reaction Time (SC, n = 834, processing speed), and Word Pairs (WP, n = 916, associative memory). Testing procedures and quality control measures for these tasks are described in [2]. We used performance and mean Reaction Time (RT) data if available. Language features were extracted using the Linguistic Inquiry and Word Count (LIWC, https://www.liwc.app/) program and idea density via CPIDR [3]. LIWC features were general language style (i.e., word count, pronoun use, numbers, long words) and features specific to spoken language, (filler words ("you know") and non-fluencies ("eh")). Idea density measured how many ideas are expressed, controlling for the amount of words used. We correlated language features with tasks. [2] https://dx.doi.org/10.17504/protocols.io.14egnyqw6v5d/v1
[3] https://doi.org/10.3758/BRM.40.2.540

Results: We found that both idea density (FLK: r = -.19; LNswitch: r = -.15; SCchoice: r = -.17), and word count (FLK: r = -.19; LNswitch: r = -.15; SCchoice: r = -.17) were significantly correlated with RTs but not performance across tasks. Use of first-person pronouns (I-talk) was significantly correlated with RTs in FLK (r = .14) and SCchoice (r = .15). Fillers and non-fluencies were not correlated with task, and neither was use of numbers or long words.

Conclusions: Our results show that aspects of spoken language can track cognitive functioning, specifically verbosity, how many words participants produced, and idea density, how many ideas they expressed, with higher values indicating faster RTs. This was true across different tasks, suggesting an underlying general language factor that could reflect EF. More I-talk, linked to depression in past work [4], indicated lower RTs and therefore, lower inhibition and processing speed. The lack of association of cognition with hallmarks of spoken language (i.e., fillers or non-fluencies), could be a methodological artifact, stemming from the use of AI-generated transcripts rather than human-generated transcripts. Our work demonstrates the potential of natural spoken language, as collected with a standardized free recall speech task, to give rise to EF and cognition more broadly. [4] https://doi.org/10.1037/pspp0000187

MIDDLE TEMPORAL GYRUS TRANSCRIPTOMICS REVEAL DISTINCT GLIAL, NEURONAL, AND REGULATORY ALTERATIONS IN ALZHEIMER'S DISEASE AND NORMATIVE AGING.
Piras IS, Bonfitto A, Song S, Aldabergenova A, Sloan J, Trejo A, Troncoso JC, Geula C, Rogalski EJ, Kawas CH, Corrada M, Beach TG, Serrano GE, Paul WF, Barnes CA, Huentelman MJ. Translational Genomics Research Institute; Johns Hopkins University; Northwestern University; University of Chicago; University of California, Irvine; Banner Sun Health Research Institute; Johns Hopkins University; University of Arizona; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is characterized by amyloid-β plaques, neurofibrillary tangles, and neuronal dysfunction. Normative aging shares partially overlapping processes, including neuronal transcriptional downregulation and glial activation. Here we profiled postmortem middle temporal gyrus (MTG) samples with bulk RNA-sequencing to characterize transcriptional changes associated with AD and normative aging.

Methods: Fresh-frozen MTG samples were analyzed by bulk RNA-seq from 217 clinically and neuropathologically confirmed AD cases and 290 with no-dementia controls (CTL) aged ≥65 years. Aging analyses were performed in CTL spanning adulthood (24–108 years; n = 324), including a subset aged ≥65 years (n = 299). We used DESeq2 for differential expression, MEGENA for coexpression analysis, SCENIC for regulon activity, and Matrix-eQTL for expression quantitative trait loci (eQTL).

Results: We identified 613 AD-associated differentially expressed genes (DEGs), with NPNT and ADAMTS2 among the top signals. AD was characterized by reduced excitatory neuronal gene expression and increased microglial, astrocytic, endothelial, and pericyte programs, together with activation of angiogenesis, extracellular-matrix (ECM) organization, adaptive immunity, and suppression of neuronal and mitochondrial processes. Coexpression analysis identified three disease-associated modules: a neuron-mitochondrial module suppressed in AD (M5; GABRB3), a microglial immune module upregulated in AD (M6; FCER1G), and an astrocyte-vascular ECM module increased in AD (M8; TAGLN). eQTL analysis indicated limited genetic contribution to AD transcriptional signatures. Eighteen regulons showed differential activity in AD, with targets enriched in modules reflecting neuronal suppression and astrocyte/ECM activation.

Aging (24–108 years) was associated with decreased expression of genes involved in translation, proteostasis, and mitochondrial function, and increased oligodendrocyte and myelination programs. In the 65+ subset, neuronal and protein-folding modules showed the strongest decreases, while glial upregulation was attenuated. Thirteen age-associated regulons overlapped significantly with coexpression modules linked to oligodendrocyte/myelin remodeling and reduced proteostasis.

Conclusions: Late-life aging is characterized by glial responses and neuronal/proteostasis suppression, whereas AD additionally involves immune, vascular, and ECM activation with stronger repression of neuronal programs. Concordance between TF regulons and coexpression networks reveals regulatory structure underlying these processes, while limited enrichment of common-variant eQTL targets suggests a modest contribution of genetic variation to transcriptional changes.

ENDOGENOUS DOUBLE-STRANDED RNA TRIGGERS CHRONIC STRESS IN AGED NEURONS. Rhine K, Epstein E, Carlson NM, Mumford S, Ge X, Mizrahi O, Pulliam SE, Kopalle HM, Kamat A, Hermann A, Brothers WR, Ravits J, Bennett EJ, Pekkurnaz G, Yeo GW. University of Arizona; University of California, San Diego; Arizona Alzheimer's Consortium.

Background: The integrated stress response (ISR) is the cell's primary defense mechanism against a wide variety of molecular insults, including viral infection, starvation, and the accumulation of unfolded proteins. In stressed conditions, stress responsive kinases will phosphorylate the initiation factor eIF2α, halting the translation of most proteins. The subsequent release of ribosome-associated mRNA leads to the formation of biomolecular condensates called stress granules, which sequester RNA and RNA-binding proteins (RBPs). Once the stress event has passed, stress granules dissolve and general translation resumes. Overall, the ISR is highly responsive to the cellular environment, activating within minutes of stress exposure and returning to baseline conditions within an hour. Neurodegenerative diseases are linked with dysregulation of the integrated stress response (ISR), but there is significant disagreement about which stress might contribute to aging and neurodegenerative diseases like Alzhiemer's.

Methods: Here, we leverage directed transdifferentiation of human fibroblasts into aged neurons to determine the source of ISR activation through imaging, sequencing, biochemical approaches, and other methods. We transdifferentiate donor fibroblasts directly into neurons. Transdifferentiation bypasses the pluripotent stem cell state, and transdifferentiated neurons retain key aging markers like altered CpG methylation, expression of senescence and apoptotic markers, and upregulation of aging-associated immune pathways. Our transdifferentiation strategy relies on inducible exogenous overexpression of the neurotrophic transcription factors NGN2 and ASCL1 in conjunction with small molecules that antagonize fibroblast cell fates and promote neuronal maturation. We confirm key results in postmortem brain tissue.

Results: We demonstrate that increased accumulation of cytosolic double-stranded RNA (dsRNA) activates the eIF2α kinase PKR, which in turn triggers the ISR in aged neurons and leads to sequestration of dsRNA in stress granules. Aged neurons accumulate endogenous mitochondria-derived dsRNA that directly binds to PKR. This mitochondrial dsRNA leaks through damaged mitochondrial membranes and forms cytosolic foci in aged neurons. Finally, we demonstrate that PKR inhibition leads to the cessation of stress, resumption of cellular translation, and restoration of RNA-binding protein expression. Meanwhile, exposure to new, artificial stress leads to expression of Alzheimer's disease-linked cryptic exons and failure to express stress-responsive protein chaperones.

Conclusions: Together, our results identify a source of RNA stress that destabilizes aged neurons and may contribute to neuronal variability. Exposure to future stress events or other stimuli could promote the onset of Alzheimer's disease, explaining why aging is such a potent risk factor for neurodegeneration.

MODELING ALZHEIMER'S DISEASE USING APOE E4/E4 AND SERUM-EXPOSED HUMAN CEREBRAL ORGANOIDS. Song S, Sloan J, Nicholson L, Mosqueda M, Venkatachalam H, Serrano GE, Huentelman MJ, Piras IS. Translational Genomics Research Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) pathology emerges from interactions between genetic risk, systemic/peripheral factors, and brain cells-type dysfunctions, and this biological complexity has limited the discovery of disease-modifying therapeutics.

Methods: To address the need for experimental platforms capable of modeling AD at human-specific resolution, we generated two AD cerebral organoids (AD-CO) models using 1) CRISPR modified WTC-11 iPSCs carrying APOE e4/e4 and 2) wild-type (WT) WTC-11 iPSCs with APOE e3/e3 genotype exposed to serum derived from four AD donors of both sexes, provided by the Banner Brain and Body Donation Program. Serum exposure was performed from day (D) 75 to D87. Control (CTL) COs were developed from WT WTC-11 without serum exposure. We performed immunofluorescence staining using antibodies against phospho-Tau (pTau), total Tau, and amyloid Beta (ABeta), and performed RNA-seq at D87 to identify transcriptional changes.

Results: We observed increased pTau, Tau and ABeta levels in both AD-COs with APOE e4/e4 and AD-CO serum exposed compared with CTL-CO. Differences were significant for pTau in APOE e4/e4 AD-CO ($P < 0.01$) and for both AD-COs for Tau ($P < 0.05$). RNA-seq revealed 1,075 Differentially expressed genes (DEGs) in serum-exposed AD-COs relative to CTL-CO. Upregulated pathways included immune, translation, and extracellular matrix related processes, while downregulated pathways included synaptic and neurotransmitter-related functional classes. AD-CO DEGs were significantly enriched for AD-associated signatures across multiple brain regions, such as the temporal cortex (TCX) and parahippocampal gyrus (PHG). APOE e4/e4 AD-COs versus CTL-CO analysis identified 304 DEGs, with upregulation of mitochondrial pathways and downregulation of synaptic processes. The transcriptomics profiles showed an enrichment for AD post-mortem brain signatures in TCX, PHG, and superior temporal gyrus.

Conclusions: In conclusion, our organoid models recapitulate AD-relevant molecular signatures. Future steps will include generating patient-derived COs and assessing their genomic and transcriptional concordance with matched post-mortem brain tissue to further validate this personalized human CO platform.



Institutional Information

Research Summaries and Key Personnel From Each Participating Institution

ARIZONA STATE UNIVERSITY

Over a decade ago, ASU set forth to redefine the landscape of higher education by focusing on a model of the New American University. ASU is recognized globally as a leading knowledge enterprise, and is committed to delivering academic excellence, advancing research-based solutions for humankind's greatest challenges, and producing strong and compassionate leaders. With swift momentum, ASU has led the world with innovative ideas to student-centric public higher education, honing in on academic excellence, the highest quality education and training, inclusiveness to a broad demographic, and maximum societal impact. Underscoring this exemplary new path, ASU has been ranked number one for innovation by U.S. News and World Report for the last eleven years (2016-2026), and number 1 in the U.S. and top 10 in the world for global impact in research, outreach, and stewardship by Times Higher Education for six years (2020-2025). With Alzheimer's disease (AD) affecting roughly one in nine people 65 years old and over, and one in three people 85 years old and over, research on AD and AD-related dementias (ADRD) exemplifies the types of endeavors that ASU seeks to promote, and a focus on innovative and impactful approaches is most certainly critical to associated research and treatment efforts.

For the Arizona Alzheimer's Consortium, ASU helps provide the Outreach and Recruitment Core (Dr. David W. Coon) and Research Education Component (Dr. Heather A. Bimonte-Nelson) which serve researchers throughout the state as part of the Consortium's NIA-sponsored Arizona Alzheimer's Disease Research Center. The ASU team includes scientific leaders and collaborative science discovery approaches that span molecular to behavioral outcomes across multiple species in aging, AD, and ADRD. Our approaches to aging, AD, and ADRD research leverage collaboration and team-based science, as it is acknowledged the multi-dimensions of discovery are optimally approached by acknowledging the vastness, interconnectedness, depth, breadth, and complexity of the problem at hand. Research includes basic, translational, and clinical approaches to: develop AI-assisted retinal vascular analysis methods to identify preclinical AD-related microvascular alterations in APOE4 carriers and investigate relationships between retinal GP-derived fractal measures and cognitive function (Wang laboratory); utilize magnetic resonance electrical conductivity imaging to produce quantitative maps that enable the early identification of subtle brain alterations as structural and cognitive damage begins, thereby establishing a more sensitive clinical tool for detecting early brain abnormalities (Sadleir laboratory); quantify micro- and nano-plastics in the aging brain and associate with AD pathology (Mastroeni laboratory); decipher whether age- and surgical menopause- associated brain changes in activity dependent protein expression coincide with altered glial activation, as well as patterns of myelination and oligodendrocyte turnover (Newbern laboratory); characterize tau evolution during normal brain aging by identifying tau post-translational modifications, and dissecting molecular mechanisms by which tau impacts microtubule structure and mitochondrial dynamics to define early cellular changes that precede neurodegeneration, thereby yielding insight into shifts from normal aging to AD (Tseng laboratory); identify pathologies in the cerebellum associated with AD with evaluations spanning preclinical translational modeling to humans, including associating genetic contributions to cerebellar structure, perineuronal nets, and cognition (Verpeut laboratory); provide critical insight into how a recently identified rare variant in RELN (H3447R), (RELN-COLBOS), modifies AD risk, informing future therapeutic strategies for neuroprotection (Brafman laboratory); use aging and AD tissue and organoids to determine metabolic dysregulation in degeneration, including deciphering how metabolic programs are altered during degeneration onset sporadically across aging, and how genotype affects metabolism and degeneration onset in patient-derived cell models (Andrews laboratory); decipher the

effects of menopause-associated hormone receptor modulating therapies on learning, memory, and neural plasticity during aging (Bimonte-Nelson laboratory); and assess the impact of a Zoom-based delivery of skills training and care planning intervention to address the concerns of family caregivers of people with Down Syndrome or another intellectual disability who are developing ADRD as they age (Coon laboratory).

It is noteworthy that ASU has numerous scientific research domains that are being further developed and strengthened to bolster the impact on AD, ADRD, and aging research, with a focus on discovery and action to move trajectories, diagnosis, treatment, and care forward. These include, but are not limited to, the neurosciences, health outcomes research, and focused translational research realms that pose hypothesis-driven questions approached from a systems and interdisciplinary perspective. Collectively, ASU has a solid framework and wide-ranging strengths that are poised to make great strides in the scientific fight against AD, to optimize the trajectory of brain aging using both preclinical and clinical approaches, and to advance care, caregiving models, and interventions that enhance the quality of life of people living with AD and their informal caregivers. Moreover, it is noteworthy that the assets in the research programs at ASU within the Arizona Alzheimer's Consortium represent a large range of colleges, institutes, and centers across ASU.

ASU and Phoenix-based Banner Health, one of the nation's largest nonprofit health systems, have launched a research alliance which includes the establishment of the Neurodegenerative Disease Research Center (NDRC)[1]. The NDRC, directed by Dr. Jeffrey Kordower, is envisioned to become one of the world's largest basic science centers for the study of AD and other neurodegenerative diseases. The NDRC is advancing the discovery of disease mechanisms, risk factors, biomarkers, and drugs for the understanding, detection, tracking, treatment and prevention of neurodegenerative diseases. It is expected to continue to grow to include about 20 new laboratories and additional affiliated laboratories. It fosters push-pull relationships between big data and other analyses of post-mortem and other human data sets, as well as experimental models. Notably, the NDRC leverages collaborations amongst several consortium partners to provide a public resource of detailed omics data from different cell types and regions in clinically and neuropathologically characterized brain donors. The NDRC is intended to further clarify disease mechanisms and risk factors for AD and related disorders, provide new therapeutic targets, and support the discovery of new treatments and biomarkers.

A strength of ASU is the training, mentoring, and education of future generations of aging and neurodegenerative disease researchers and academicians, spanning high school students, to undergraduate students, to graduate students, and to postdoctoral fellows. The approach to training is hands-on, multifaceted, and interdisciplinary, with the goal to engage future scientists and the next generation of scientific leaders in aging and neurodegenerative research to yield maximal impacts on research discovery and translational outcomes. The ADRC Research Education Component, co-directed by Dr. Heather Bimonte-Nelson (ASU) and Dr. Gerson Hernandez (U of A), reflects this strong and extensive training commitment. Notably, ASU offers graduate degrees in Statistics and Biomedical Informatics, the Behavioral Neuroscience and Comparative Psychology Program[2] within the Department of Psychology, as well as the Interdisciplinary Graduate Program in Neuroscience, which is a collaborative effort between ASU, Barrow Neurological Institute, the University of Arizona College of Medicine – Phoenix, and the Translational Genomics Research Institute (TGen)[3]. The latter two training programs focus upon approaches that integrate multiple levels of analysis using systems and interdisciplinary approaches – molecular, cellular, behavioral, and cognitive – to address preclinical, clinical, and translational questions about brain and behavior relationships.

[1] https://biodesign.asu.edu/neurodegenerative-disease/
[2] https://psychology.asu.edu/degrees/specializations/behavioral-neuroscience-comparative-psychology
[3] https://sols.asu.edu/degree/graduate/neuroscience-phd

ARIZONA STATE UNIVERSITY

Key Personnel

Name (last, first)	Degree	Role on project
Andrews, Madeline	PhD	Project PI, Assistant Professor
Anyigbo, Kamdikachukwu		Undergraduate Student
Asuncion, David Leonard	BS	MS student, data analysis and student advisor
Azferene Naqvi, Syeda		Undergraduate Student
Bakyt, Akbota		Undergraduate Research Assistant
Behera, Shanak		Undergraduate Research Assistant
Belthur, Meghana		Undergraduate Student
Berkley, Aaron		Undergraduate Research Assistant
Bhirisha Sharma	BPharm	Graduate student
Billingsley, Kenndal	BS	Graduate Researcher
Bimonte-Nelson, Heather	PhD	PI & Co-Investigator - President's Professor of Psychology
Bjorklund, George	PhD	Research Scientist
Brafman, David	PhD	PI, Project Collaborator, Professor
Carll, Phil	MS	Research Specialist/Interventionist
Christiansen, Kendall		Undergraduate Research Assistant
Coon, David W.	PI	Director, Center for Innovation in Healthy and Resilient Aging
Corbin, Sierra		Undergraduate Student
Cordorva, Lourdes		Promotora
Diaz, Zamira		Undergraduate Student
Dong Xuanzhao	MS	Graduate Researcher
Doyle, Rhys	BS	Research Technician, Laboratory Manager
Essuman, Albert	MS	Graduate Researcher
Finnen, Hilary	BS	Research Specialist
Frisch, Caryle	PhD	Postdoctoral Researcher
Furukawa, Tiara		Undergraduate Research Assistant

Name (last, first)	Degree	Role on project
Garayzar Lopez, Angela		Undergraduate Student
Glinka, Allison	MS	Project Coordinator
Gomez-Morales, Abigail	PhD	Assistant Professor
Gonzales-Pyles, Maria Socorro		Research Specialist/Interventionist
Gonzalez-Cruz, Isabella		Undergraduate Student
Graf, Rose	BS	Research Specialist
Gray, Kayla	MS	Knowledge Donor Project Liaison
Gu, Haiwei	PhD	Project Collaborator, Associate Professor
Hannahs, Marisa		Undergraduate Student
Hashim, Aliya		Undergraduate Research Assistant
Highton, Lynn		Undergraduate Student
Holappa, Inkeri		Undergraduate Student
Jason Newbern	PhD	PI - Associate Professor
Jolly, Rahila		Undergraduate Research Assistant
Kalas, Samantha		Undergraduate Student
Kaur, Ishmeet		Undergraduate Student
Kling, Juliana	MD	Co-Investigator – Chair of Women's Health and Professor of Medicine
Krishnan, Talin		Undergraduate Research Assistant
Law, Olivia	BS, MS	Graduate Research Assistant
Lee, Briana		Undergraduate Research Assistant
Leyasi, Salma	BS	Graduate Researcher
Li, Xin	MS	Graduate Researcher
Lizik, Camryn	MA	Graduate Student
Lyle, Tristan	BS, MS	Graduate Research Assistant
Mastroeni, Diego	PhD	Principal Investigator
Maze, Sharmeen	MS	MRI Research Technologist (KD scanning at BNI)
Melick, Alexandria	BS, MS	Graduate Research Assistant
Mufson, Elliott	PhD	Co-I
Neyts, Sam	BS	MS Student

Name (last, first)	Degree	Role on project
Nguyen, Mia	BS	Graduate Researcher
Nukala, Tara		Undergraduate Research Assistant
Oevermann, Matthew	MA	Graduate Student
Ortega, Tydan		Undergraduate Research Assistant
Perez, Sylvia	PhD	Co-I
Raghavan, Indu	PhD	Postdoctoral Researcher
Readhead, Benjamin	MBBS	Co-Investigator
Rostami, Mantra	BS	Graduate Research Assistant
Roulinavage, Keean		Undergraduate Research Assistant
Rudha, Qamar		Undergraduate Research Assistant
Sadleir, Rosalind	PhD	PI, data analysis, scientific director
Santos, Sydney	BS	Research Specialist/Interviewer
Simmons, Amberlyn	PhD	T32 Postdoctoral Fellow
Tseng, Jui-Heng	PhD	Principal Investigator
Verpeut, Jessica	PhD	PI
Wang, Yalin	PhD	Professor
Woodruff, Bryan	MD	Medical Advisor
Xiong, Yujian	MS	Graduate Researcher
Yamada, Nelson	BS	Graduate Research Assistant
Yerramilli, Adhiti		Undergraduate Research Assistant
Zhou, Yuxiang	PhD	Sequence Design, Analysis, GE Liaison

BANNER ALZHEIMER'S INSTITUTE - PHOENIX

As the first Center of Excellence at Banner Health, the Banner Alzheimer's Institute (BAI) was established in Phoenix in 2006 to achieve several ambitious goals: 1) To find effective Alzheimer's prevention therapies without losing a generation; 2) To establish a new standard of care for patients and family caregivers; 3) To galvanize the fight against Alzheimer's and related diseases in other ways; and 4) To forge models of collaboration in biomedical research.

BAI has made pioneering contributions to the unusually early detection, tracking, study and diagnosis of Alzheimer's, the discovery of genetic and non-genetic risk and protective factors, disease mechanisms, promising modifying and prevention therapies, the validation of brain imaging methods and blood tests for the diagnosis of Alzheimer's and related disorders, and the accelerated evaluation of disease-modifying and prevention therapies. It launched a new era in Alzheimer's prevention research, introduced many research paradigms, methods and trials needed to accelerate the evaluation and approval of effective prevention therapies, and established several collaborative paradigms and resource sharing programs to have the greatest impact.

BAI's ongoing efforts have given the field a chance to find effective secondary prevention therapies in cognitively unimpaired persons with biomarker evidence of amyloid plaques by end of 2026, extend therapies to be administered at home by end of 2027 and identify primary prevention therapies in cognitively unimpaired persons at genetic risk who do not yet show biomarker evidence of amyloid plaques – by end of 2028. Its medical, clinical, family and community services program, and wide range of education, outreach and support programs have established a best-in-class approach to the care of patients and their families, and it has implemented approaches to extend its impact to the primary care setting and underserved communities. It has found impactful ways to complement, enhance, and benefit from close working relationships with organizational partners inside and outside of the Arizona Alzheimer's Consortium (AAC).

The Stead Family Memory Center at BAI-Phoenix includes a Memory Clinic, Family and Community Services Program and Clinical Trials Program. It offers a wide range of services for the evaluation and care of affected persons and family caregivers, helping to address their medical and non-medical needs throughout the diagnosis and course of disease. It provides educational, outreach and research awareness programs for Arizona's Native American and Hispanic/Latino communities, including their enrollment in our National Institute on Aging (NIA)-sponsored Arizona Alzheimer's Disease Research Center's (ADRC's) Clinical Core, and organizes an annual conference on Alzheimer's disease and related disorders in Native Americans. Its Banner Dementia Care Program is a population health model that utilizes specially trained health coaches to provide education, skill-building, support, and resources to help individuals living with memory loss and their caregivers live well and improve quality of life throughout Arizona.

BAI conducts numerous clinical trials of investigational treatments, observational clinical studies and research registries, including many led by researchers within the Alzheimer's Prevention Initiative (API). Its researchers, in collaboration with partnering organizations, oversee an NIA-sponsored cohort study of cognitively unimpaired persons across all six *APOE* genotypes , which has helped to conceptualize the preclinical stages of AD, an NINDS-sponsored study of chronic traumatic encephalopathy (CTE) in former National Football League and college football players, and one of the Precision Medicine Initiative's (PMI's) first healthcare provider-led cohort programs in a partnership between University of Arizona and Banner Health. It has begun to capitalize on a shared resource of blood samples, longitudinal data and post-mortem neuropathological data at Banner Sun Health Research Institute (BSHRI) to support the head-to-head comparison of emerging blood biomarkers in the diagnosis and study of Alzheimer's and related disorders.

BAI's state-of-the-art NOMIS Brain Imaging Center includes two PET/CT systems, a 3T MRI, cyclotron, radiochemistry laboratory, and computational image analysis laboratory. It provides imaging resources and expertise, research PET tracers, image-analysis methods, data and biological samples for researchers inside and outside of Arizona. Its researchers, facilities and resources support numerous clinical and observational trials, including a longstanding collaboration with Mayo Clinic for the above-mentioned NIA-sponsored longitudinal brain imaging study of cognitively unimpaired persons across all six *APOE* genotypes, and image-analysis techniques with improved power to characterize subtle brain changes over time. Its researchers collaborate with the University of Antioquia and Massachusetts General Hospital for studies of PSEN1 E280A mutation carriers and non-carriers from the world's largest autosomal dominant Alzheimer's disease (ADAD) kindred in Colombia. BAI researchers were founding members of the Alzheimer's Neuroimaging Initiative (ADNI) PET Core, in which it was responsible for the development, testing and use of voxel-based image analysis techniques with improved power to detect and track AD. AAC funds complement research activities supported by competitive grant awards from NIA, private foundation grants and clinical trials. Imaging and other data and image-analysis techniques from BAI's NIA-sponsored ADRC and studies of cognitively normal APOE4 carriers and non-carriers provide a core resource for interested investigators inside and outside of Arizona.

BAI-Phoenix, BAI-Tucson, BSHRI, and its partners have begun to place a growing emphasis on the acquisition of antemortem brain-imaging, cerebrospinal fluid (CSF) and blood biomarkers for Alzheimer's and related disorders in their longitudinal cohorts to find and support the use of promising amyloid and other blood tests for Alzheimer's and related disorders. These partner organizations, TGen, and ASU (e.g., at the ASU-Banner Neurodegenerative Disease Research Center [NDRC]) have also developed a shared resource of DNA and RNA sequencing data from different brain cell types and regions in high-quality brain samples from Alzheimer's cases and controls and have used big data analytical techniques to characterize networks and drivers at which to target in the discovery of new treatments.

With several hundred million dollars in NIH, philanthropic and industry support, BAI's API has helped make it possible to find and support the approval and availability of Alzheimer's prevention therapies far sooner than otherwise possible. It includes a growing number of prevention trials in persons who, based on their genetic and/or biomarker findings, are at increased risk for Alzheimer's, including the very first prevention trial in Colombian members of the world's largest ADAD kindred, who are virtually certain to develop the disease and become cognitively impaired at the median age of 44. API launched its second trial in this Colombian kindred in mid-2026. Its ongoing prevention trial of a recently established amyloid plaque-clearing antibody therapy, performed in partnership with Eli Lilly, has a realistic chance to find an effective prevention therapy in 2026 or 2027, and other prevention trials of a next generation antibody therapy are on the way. These and other trials are intended to evaluate the investigational treatments in potentially license-enabling prevention trials, support the qualification of biomarker endpoints likely to be associated with a clinical benefit in prevention therapies and provide a shared resource of data and biological fluids for the research community after the trials.

BAI's Alzheimer's Prevention Registry (www.endALZnow.org) has provided updates about advances in prevention research and opportunities to enroll in Alzheimer's related trials to nearly 400,000 individuals; its GeneMatch Program (www.endALZnow.org/genematch) has characterized APOE genetic test results in more than 100,000 of these participants, provided a resource of interested research participants to Alzheimer's -focused studies. Its researchers have developed suitable ways to inform individuals about their APOE-related risk and/or biomarker findings. It continues to champion new ways to identify and support enrollment in prevention trials (e.g., using blood biomarker tests), and address the logistical, ethical and scientific issues involved in this endeavor.

BAI's organizational aims include:

1. To leverage imaging, CSF and emerging blood biomarker resources in the early detection, tracking, and diagnosis of Alzheimer's and related disorders, the clarification of genetic and non-genetic risk factors, and other collaborative research studies inside and outside of Arizona.

2. To leverage imaging resources in the early detection and tracking of related diseases (e.g., chronic traumatic encephalopathy [CTE]).

3. To provide resources needed to develop and test novel PET radiotracer techniques for the assessment of Alzheimer's and related disorders.

4. To further develop PET and MRI image-analysis techniques with improved power to detect and track Alzheimer's and evaluate disease-modifying and prevention therapies.

5. To accelerate and inform the evaluation, approval, and accessibility of Alzheimer's prevention therapies and the emerging blood biomarkers, cognitive tools, and risk disclosure methods needed to inform their use.

7. To help provide the blood samples, imaging methods and (with BSHRI) post-mortem neuropathological assessments needed to characterize and compare the accuracy of emerging blood tests for the diagnosis of Alzheimer's and related disorders, and to establish the generalizability of these methods to persons from Arizona's Hispanic/Latino and Native American communities.

9. To advance the science of research participant engagement and study participation, including in individuals at highest risk for Alzheimer's and related disorders.

10. To share data and biological fluid samples with the research community, establish a public resource of blood samples from thousands of well-characterized persons, help the field develop and test blood tests for Alzheimer's and related disorders as soon as possible, advance the roles of blood biomarkers in research, treatment evaluation and clinical care, and advance the complementary research goals of our partners inside and outside Arizona.

11. To provide a care model that more fully addresses the needs of patients and families and BAI, including via its Dementia Care Partners program.

12. To support the clinical research and Native American outreach, education and enrollment goals of the Arizona ADRC.

13. To promote further development, productivity, and close working relationships of research programs involved in the fight against Alzheimer's and related disorders.

BANNER ALZHEIMER'S INSTITUTE – PHOENIX

Key Personnel

Name (last, first)	Degree	Role on project
Alexander, Robert	MD	Chief Scientific Officer, Alzheimer's Prevention Initiative
Al-Sahlani, Heba		PA – Specialty Care, Neurology
Amador, Ricardo		Clinical Research Program Manager
Autry, Lynn		Senior Psychometrist
Basham, Courtney		Clinical Research Assistant
Battraw, Angelena		Clinical Research Coordinator
Bauer lll, Robert		Senior IT Systems Analyst
Blake, Lauren	PsyD	Neuropsychologist
Boker, Constance		Director, Imaging Center
Brown, Christopher		Senior Research Data Program Manager
Buco, Richmond Andre		Senior Psychometrist
Cardenas, Melanie		Clinical Research Assistant
Casper, Corey	MD, MPH	Senior VP, Chief Research Officer
Chen, Yinghua		Data Scientist
Copeland, Jacquie	PhD	Neuropsychologist
Colvin, Deidra		Events Coordinator
Crossland, Annamaria		Clinical Research Coordinator
Diaz, Christina		Clinical Research Recruitment Program Manager
De Santiago, Diana		Senior Clinical Research Program Manager
Devadas, Vivek		Data Analyst
DiLise-Russo, Marjorie		Senior Psychometrist
Enos, Jessica		Senior Clinical Research Program Manager
Erickson, Claire	PhD	Staff Scientist
Eviston, Sophia		Clinical Research Coordinator
Ghisays, Valentina	PhD	Bioinformatics Scientist
Gopalakrishna, Ganesh	MD	Associate Director, Memory Clinic
Goradia, Dhruman	PhD	Bioinformatics Scientist
Gordon, David		Global Projects Program Director
Henderson, Rachel		Senior Manager, Clinical Trials
High, Nellie		Senior Clinical Research Recruitment Program Manager
Jaeger, Chad		Senior Director, COO Banner Research
Joshi, Pallavi	MD	Physician - Dementia
Knox, Jennifer		Clinical Research Coordinator
Koren, Andrei	PhD	Associate Director, Radiochemistry Lab
Langbaum, Jessica	PhD	Senior Director, Alzheimer's Prevention & Research Principal Investigator and Director, Arizona Alzheimer's Disease Research Center

Name (last, first)	Degree	Role on project
		(ADRC), co-Leader, Outreach, Recruitment and Engagement Core
Langlois, Carolyn		Associate Director, API Programs & Research
Lee, Wendy		Senior Manager, Research Bioinformatics
Lerner, Marcy		Clinical Research Assistant
Li, Shan		Associate Bioinformatics Analyst
Liang, Winnie	PhD	AAC Administrative Director, Arizona ADRC Administrative Director
Lomay, Nicole		Senior Outreach Program Manager
Luo, Ji		Data Scientist
Lydiard, Renee	NP	NP – Specialty Care, Neurology
Malek Ahmadi, Michael	PhD	Senior Bioinformatics Scientist
Martinez, Laura		Senior Clinical Research Coordinator
Mulder, Heather		Associate Director, Outreach Research
Nisson, Lori	MSW/ LCSW	Director, Family & Community Services
Ochoa, Cassandra		Senior Clinical Research Recruitment Program Manager
Pandya, Sachin		Senior Manager, Clinical Trials
Parkhurst, David		Clinical Research Program Manager
Patel, Roma		Director, Clinical Trials
Perrin, Allison	MD	Physician - Dementia
Protas, Hillary	PhD	Bioinformatics Scientist
Pruzin, Jeremy	MD	Physician - Dementia
Rehban, Julia		Clinical Research Lab Coordinator
Reiman, Eric	MD	CEO Emeritus, Banner Alzheimer's Institute and Banner Sun Health Research Institute Director, Arizona Alzheimer's Consortium (AAC) Co-Director, Arizona ADRC
Salata, Haley		Senior Clinical Research Recruitment Program Manager
Schmitt, Andrea		Director, Sponsored Projects
Sohankar, Javad	PhD	Bioinformatics Scientist
Starner, Mary Kate		Clinical Research Coordinator
Su, Yi	PhD	Associate Director, Computational Brain Imaging Analysis Program; Leader, Arizona ADRC Data Management and Statistics Core; Co-leader, Arizona ADRC Biomarker Core
Tariot, Pierre	MD	Director (Emeritus), Banner Alzheimer's Institute
Tsai, Po-Heng	MD	Associate Director, Clinical Trials; ADRC BAI-Phoenix Clinical Site PI
Vadovicky, Sheila		Senior Psychometrist
Walsh, Trisha		Associate Director, Observational Research Programs
Zigler, Lisa		Senior Manager, Clinical Trial

BANNER ALZHEIMER'S INSTITUTE - TUCSON

Banner Alzheimer's Institute in Tucson (BAI-T) was established in 2019 and its goals are to end Alzheimer's disease (AD) without losing another generation, develop a new standard of patient and family care, including innovative programs to address both the medical and non-medical needs of patients and family caregivers, and provide these resources, services, and programs to Tucson and Southern Arizona. BAI-T follows the BAI-Phoenix model of providing comprehensive dementia care. This model encompasses the BAI Family and Community Services (FCS) program, the Toole Family Memory Clinic, and the J. Orin Edson Family Lewy Body Dementia Center.

BAI-T is dedicated to the early detection and treatment of Alzheimer's disease, and we are actively integrating blood-based biomarkers (p-tau217) into the diagnostic assessment of individuals with memory concerns, as well as building an active program in providing access to disease-modifying treatments (lecanemab and donanemab) for individuals with mild cognitive impairment (MCI) or early AD. Our monoclonal antibody infusion program currently has 40 active participants, including 3 patients who are receiving SQ maintenance treatment with lecanemab. An additional 59 patients are currently undergoing the required workup to determine eligibility. To date, 156 patients have been evaluated in our program. BAI-T also participates as a site for the ALZ-NET registry on monoclonal antibody therapies for AD.

The FCS program provides both educational and counseling services to families and caretakers and utilizes individual and family-based psychotherapy to relieve the distress associated with dementia, while the Toole Family Memory Clinic provides additional dementia services, including comprehensive neuropsychological evaluations, and support for individuals, caretakers, and families in Tucson and Southern Arizona. Individual and group cognitive training programs have recently been added to support patients with MCI and plans are underway to incorporate programs on prevention of cognitive decline and dementia.

The Lewy Body Dementia Center at BAI-T, led by Dr. Kathryn Bradley, has a primary focus on Parkinson's disease dementia and dementia with Lewy bodies, and is aimed at meeting the needs of patients suffering from Lewy body disease. The Center offers a Neuro Wellness program that provides community-centric wellness classes to help manage the loss of motor functions and balance, and complements current medical treatments for those affected by neurologic conditions, including movement disorders and other types of dementia.

BAI-T serves as a Center of Research Excellence in the treatment and prevention of AD and related dementias (ADRD). Its research activities are supported by the National Institute on Aging (NIA) through the Arizona Alzheimer's Disease Research Center (ADRC; P30 AG072980), the Arizona Alzheimer's Consortium (AAC) which provides funding for research led by PIs Dr. Rapcsak and Dr. Edmonds, as well as industry-sponsored clinical trials conducted at our institute. The Arizona ADRC is a statewide collaborative research program that is dedicated to the early detection, diagnosis, tracking, treatment, and prevention of AD and ADRD. The Arizona ADRC enrolls and longitudinally follows a cohort of well-characterized research participants ranging from cognitively normal elderly persons to individuals at different stages of the AD continuum (preclinical, MCI, and dementia). Participants undergo detailed cognitive assessments annually and the study also includes the collection of imaging (MRI, amyloid and tau PET) and fluid biomarkers (CSF and blood), as well as genetic testing. Individuals enrolled in the study also have the option of participating in Banner Sun Health Research Institute's (BSHRI's) Brain Donation Program which provides detailed post-mortem neuropathological examination. Clinical and cognitive data, biospecimens, and genomic data collected by the Arizona ADRC are shared with other investigators through the National Alzheimer's Coordinating Center (NACC), National Cell Repository for

Alzheimer's Disease (NCRAD), and NIA Genetics of Alzheimer's Disease Data Storage Site (NIAGADS). Currently, BAI-T follows a cohort of 69 active ADRC research participants, approaching our total target recruitment goal of 75 participants. An important goal for the ADRC is to increase the participation of individuals from underserved and understudied minority groups, including Arizona's Hispanic/Latino and Native American communities. Consistent with this commitment, and with support from the AAC, BAI-T launched a partnership with El Rio Health, one of the largest primary care networks in Southern Arizona, to facilitate early diagnosis of AD in primary care by integrating p-tau217 biomarker testing into clinical practice and improve timely access to disease-modifying treatments. Our efforts in the past year have substantially increased clinical detection rates for early-stage AD in primary care settings. Prior to implementation, no p-tau217 tests were ordered by El Rio providers. Since the start of our project, 246 tests have been ordered and 144 completed, with a 53% positivity rate for AD pathology, and 28 El Rio patients were evaluated at BAI-T to determine eligibility for disease modifying treatment. Our partnership represents an important step toward reducing disparities in access to improved AD diagnosis and treatment in underserved Hispanic populations and provides a new model of AD care in the Tucson community.

Furthermore, BAI-T supports research projects initiated by BAI-Phoenix and BSHRI investigators by identifying, referring, or enrolling individuals in the Tucson community. A recent example included partnering on the NIH-funded Alzheimer's Prevention Initiative trial called Draw-10, led by Drs. Nicholas Ashton and Jessica Langbaum. BAI-T contributed 17% of the subjects enrolled in this study of short-term p-tau fluctuations and potential contributory lifestyle factors.

An important research mission for BAI-T is to identify opportunities for collaboration with investigators at the University of Arizona (UA) interested in studying AD/ADRD. We have been successful in launching several NIH-funded collaborative research projects between BAI-T and UA with Drs. Rapcsak and Edmonds serving as Co-Investigators. Examples include studies on the use of non-invasive brain stimulation (TMS) to improve memory function and hippocampal plasticity in MCI, using smart phone-based technology to track autobiographical thought as an early cognitive marker of AD, and developing new imaging methods to identify early changes in thalamic nuclei in neurodegenerative disease. We were also recently awarded another 5-year R01 grant focusing on the use of semantic memory assessment to identify early AD pathology, and have an ongoing collaboration with UA researchers on the use of noninvasive brain stimulation to improve language function in logopenic primary progressive aphasia (PPA) funded by the AAC.

In addition to these studies, BAI-T investigators Drs. Allan Anderson and Matthew Malone currently conduct 4 clinical trials. These studies include a Phase III Eli-Lilly remternetug trial (J1G-MC-LAKI) for preclinical and early AD; two Phase III Eli-Lilly donanemab trials (I5T-MC-AACI and I5T-MC-AACM) comprised of Trailblazer 2 for treatment of early AD and Trailblazer 3 for prevention or delay of onset of AD in high-risk patients; and a Phase II TargetTau-1 Clinical Trial with Bristol Myers Squibb for patients with early AD, which is the first anti-tau study conducted at our institute.

BANNER ALZHEIMER'S INSTITUTE – TUCSON

Key Personnel

Name (last, first)	Degree	Role on project
Anderson, Allan	MD	Physician – Dementia Specialist
Antoniou, Victoria	BS	Clinical Research Coordinator
Ashish, Dev	PhD	Clinical Neuropsychologist
Bradley, Kathryn	MD	Physician – Movement Disorders Specialist
Edmonds, Emily	PhD	Clinical Neuropsychologist
Malone, Matthew	DO	Physician – Dementia Specialist
Martin, Sarah	MS-NP	Nurse Practitioner – Specialty Care, Neurology
Menchola, Marisa	PhD	Clinical Neuropsychologist
Parker, Cheryl	MS-FNP	Nurse Practitioner – Specialty Care, Neurology
Rapcsak, Steven	MD	Physician – Dementia Specialist
Robinson, Jaclyn	MD	Physician – Dementia Specialist

BANNER SUN HEALTH RESEARCH INSTITUTE

Banner Sun Health Research Institute (BSHRI) is an international leader in the fight against Alzheimer's disease (AD) and Related Disorders (ADRD), including Lewy Body Diseases (Parkinson's disease [PD], Dementia with Lewy Bodies [DLB]), Vascular Brain Injury, and Multiple Etiology Dementias (MED), as well as the study of brain/cognitive aging research and clinical care. BSHRI was established in 1986 in Sun City, Arizona, the nation's first planned retirement community. BSHRI contributes significantly to diagnostic and therapeutic advances in AD/ADRD, and profoundly impacts the scientific study of AD/ADRD, Parkinson's disease (PD), other age-related brain disorders, and healthy cognitive aging.

BSHRI encompasses: **a) Comprehensive, multidisciplinary and integrated clinical centers and programs** in cognitive, memory and movement disorders that provide coordinated world-class care and services that include subspecialist clinicians and staff from The Cleo Roberts Cognitive & Memory and Movement Disorders Clinics and Clinical Research & Trials Center, the Division of Neuropsychology, and Family and Community Services program (FCS); **b)** a **Neuropsychology Center**; **c)** the internationally renowned **Brain and Body Donation Program (BBDP)** for the study of AD/ADRD, PD, related disorders, cancer and aging; **d)** the **Center for Healthy Aging**, that includes The Longevity Longitudinal Cohort Study of cognitive aging in older individuals with over 1,700 research participants (575 active) (~70% female, 327 are ≥80 years of age, 75 are between 90-99, and 7 are 100 years or older); and a free, community service, Brain Health Check-In (BHCI) Program (>1,400 performed since December 2018) to provide walk-in or scheduled brain health assessments along with feedback, information, education, resources and referrals; **e) BSHRI Fluid Biomarker Program** (consisting of the Michael T. Zuendel Family Biomarker Laboratory and The Kuhle Family Biomarker Discovery Laboratory), established in 2024 through successful recruitment of the internationally renowned AD/ADRD fluid biomarker scientist, Nicholas Ashton, PhD, to direct the state-of-the-art cutting-edge biomarker research program focused on AD, ADRD and other neurodegenerative diseases; **f)** More than 30 ongoing NIH, foundation, and biopharma-sponsored state-of-the-art **clinical trials and observational cohort studies** for AD/ADRD, PD and movement disorders and cognitive aging; **g)** Extensive **outreach, education, training and volunteer programs** including >150 lectures and education programs per year (nationally, internationally, regionally) and leadership in world-renowned continuing education programs; training in neuropsychology, cognitive neurology and movement disorders for students, residents and post-doctoral fellows; a highly productive neuroscience scholars summer research internship program for under-represented and other university students, and partnerships with Sun Health Foundation and other stakeholders in this highly concentrated community of active older adults; **h) Leadership roles and close collaborations** and relationships with AD/ADRD and movement disorders consortia, clinicians, scientists, educators, public health advocacy groups and organizations throughout Arizona and around the world. From 2001-2016, BSHRI served as the applicant organization for the AZ ADCC (Alzheimer's Disease Core Center) on behalf of the organizations in the AZ Alzheimer's Consortium, and in FY2026 Banner Health again served as the applicant organization for the grant's well-scored renewal application. BSHRI remains home to multiple consortium leaders including Drs. Alireza Atri, Geidy Serrano, Thomas Beach, Parichita Choudhury, and Nicholas Ashton.

The internationally renowned BBDP, directed by Thomas Beach, MD, PhD, and Geidy Serrano, PhD, include 690 actively followed (>5,170 enrolled since inception), clinically characterized and longitudinally assessed participants (~3,000-4,000 visits per year), including persons with AD, PD, and related disorders, and older adults with cancer or who are cognitively and neurologically unimpaired at the time of enrollment. Participants consent to donate their brains and/or bodies after death. **The BBDP continued its path in FY26 as a premier national and international research program** by adding **132 new participant donors and conducting 3,480 annual assessments in 690 living participants.** The BBDP is unique for: **a)** its rapid autopsy program (median 3.5-hour post-mortem interval) allowing

unusually high tissue quality, optimizing post-mortem discovery research on the expired donors (>2,320 autopsies performed), who have had comprehensive assessments, and biomarker collection during life and neuropathological examinations after death; **b)** a large number of brain donors who are cognitively/neurologically unimpaired at the time of enrollment, thereby advancing the study of preclinical AD/ADRD and PD and providing numerous clinically and neuropathologically normal control subjects for genetic and other research studies; **c)** whole body donation, banked organs and tissues from expired donors since 2005, and the opportunity to relate brain pathology to biological features of other body organs; and **d)** very high impact and productivity, including impactful publications, a high rate of distribution of samples and of clinical, pathological, omics and imaging data with both internal and external investigators. with annually more than 20,000-30,000 samples transferred in more than 200 requests to more than 70 different national and international investigators, together with extensive data sharing over our website platform and tailored data queries. For example, in FY26, The BBDP distributed over 206 transfers encompassing more than 30,000 biospecimens including shared samples with more than 80 Arizonan scientists (including more than 120 shipments to scientists other US states and internationally scientists); and contributed to >50 scientific publications; supported >60 grant-funded research projects and grant proposals; collected >50 skin biopsy samples, >500 blood samples and 45 cerebrospinal fluid samples, and more than 70 PET scans for amyloid plaques, tau tangles, synapses (SV2A) and/or structural brain MRI changes (>850 scans over the past 5 years at BAI Phoenix) from participants. Hundreds of BBDP participants are enrolled in the AZ ADRC's (Alzheimer's Disease Research Center's) Clinical and Ancillary BBDP Cores and the ADRC's Neuropathology Core, in partnership with Mayo Clinic AZ, Barrow Neurological Institute, BAI Phoenix and BAI-Tucson (which moved organizationally to the University of Arizona in 2026). The BBDP also plays critical roles in the neuropathological validation of amyloid-, tau- and synaptic (SV2A)-PET and other ante-mortem biomarkers, contributing to assessment and FDA approval of molecular imaging/PET, CSF and blood-based biomarkers for AD/ADRD; and provides a critical tissue resource for genome-wide genetic, transcriptomic and proteomic data from different brain regions and cell types, and to dozens of impactful research studies, collaborations, grants, and annual publications.

The BSHRI Fluid Biomarker Program, directed by Dr. Nicholas Ashton, is an internationally recognized hub for the discovery, validation, and high-throughput analysis of blood and other fluid biomarkers for AD, PD, and related neurodegenerative conditions. Launched with multi-million start-up funding, the program is structured around two complementary laboratories that together enable end-to-end biomarker development, from molecular discovery to clinical translation. The program is unique for: a) the Michael T. Zuendel Family Biomarker Laboratory, which provides centralized, high-quality assessments of fluid biomarkers across national and international clinical studies and trials, supporting early diagnosis, disease staging, and therapeutic monitoring through rigorous validation of CSF and blood-based assays—positioning the lab as a critical testing resource for research consortia and industry sponsors worldwide; b) The Kuhle Family Biomarker Discovery Laboratory, which focuses on innovation and discovery into neurodegeneration, uses advanced protein biomarker technologies and computational approaches to identify novel candidates and fluid correlates of brain pathology, which are then transitioned to the Zuendel lab in the form of clinically viable laboratory tests for clinical readiness. These two laboratories have a unique suite of cutting-edge, fully automated, high-throughput immunological platforms; including two Roche Diagnostics Cobas e801 Analyzers utilizing ElectroChemiLuminescence (ECL) technology, the Quanterix Simoa HD-X and SP-X Analyzers known for their ultra-high sensitivity and multiplexing capabilities, and the Fujirebio Lumipulse G1200, a robust chemiluminescent enzyme immunoassay (CLEIA) instrument, and two ARGO Nulisa Analysers—all supporting broad biomarker profiling, validation, and clinical translation. The laboratories' comprehensive infrastructure supports biomarker science at all stages of development—from discovery through regulatory-grade implementation—with capabilities including longitudinal sample processing, harmonized biobanking, and ultra-sensitive immunoassay development. The BSHRI Fluid Biomarker Program stands at the forefront of biomarker research and development, providing the infrastructure, scientific expertise, and

translational vision necessary to revolutionize the diagnosis and treatment of neurodegenerative diseases.

BSHRI has undergone significant changes in the last decade, shifting focus from basic sciences to clinical and translational science and biomarker and therapeutics research, and clinical and community services, and education and training programs. Changes include: **a)** Growth and harmonization with BAI on clinical, community services, clinical research and trials programs (e.g. launch and housing of the Dementia Care Partners community care navigation and support program and CMS GUIDE program through FCS; tripling the number of clinical trials, with more than 25 active AD/ADRD trials in FY26); **b)** Growth of comprehensive and integrated multidisciplinary services at The Cleo Roberts Memory and Movement Disorders Centers, including recruitment of clinicians/clinician-scientists and doubling of visit numbers – with 7,870 total clinical visits in FY26; **c)** Implementation of innovative services, clinical and research programs (e.g. the 2024 launch of the Banner-wide cutting edge therapeutic Amyloid Plaque-Lowering Monoclonal Antibody (AD-mAb) Care Patient Pathway; the BSHRI Fluid Biomarker Program, directed by Dr. Nicholas Ashton, as an internationally recognized hub for the discovery, validation, and high-throughput analysis of blood and other fluid biomarkers for AD, PD, and ADRD, and its expansion through FY26); **d)** Launch and expansion of the Brain Health Check-In (BHCI) community service program; **e)** Enhancement of clinical and biological (biofluid/serum) capabilities and characterization of the BSHRI's Longevity Study cohort (see AAC progress report, Dr. Alireza Atri PI), and harmonization and co-enrollment in the Longevity Study and BBDP programs; **f)** Growth of education, training and outreach - providing >21,000 person/hours of medical/health professional education, scientific or community lectures, presentations and programs, including co-sponsoring and co-directing (Dr. Atri) the world-renowned Harvard Medical School annual 4-day CE course (Dementia: A Comprehensive Update) and the annual 2-day BSHRI and Banner Alzheimer's Institutes CME/CE Update on AD/LBD and ADRD symposium (Directed by Dr. Choudhury) which provide cutting-edge CME/CE on AD/ADRD for local, regional, national and international clinicians; **g)** Development of a BBDP public resource of sorted cells, and omics data from different cell types and brain regions to help AZ Consortium colleagues and other researchers better clarify disease networks, and new treatment targets; and **h)** Serving as the lead institution for the Clinical Core, Biomarker Core (Co-lead), and Neuropathology Cores for the NIH (NIA)-funded AZ ADRC (P30 expanded NIH funding mechanism that replaced the AZ ADCC).

BANNER SUN HEALTH RESEARCH INSTITUTE

Key Personnel

Name (last, first)	Degree	Role on project
Al Jubouriy, Hamzah		Clinical Research Assistant
Arce, Richard		Research Data Program Manager
Ashton, Nicholas		Senior Director, Banner Research Biomarker Program
Aslam, Sidra	PhD	Bioinformatics Analyst
Atri, Alireza	MD, PhD	Director, Banner Sun Health Research Institute
Atri, Taraneh		Clinical Research Assistant
Auman, Briana	PsyD	Neuropsychologist
Beach, Thomas	MD, PhD	Director, Brain and Body Donation Program
Beh, Suet Theng	PhD	Staff Scientist
Belden, Christine	PsyD	Director, Neuropsychology
Borja, Claryssa		Senior Pathology Technician
Brown, Stephanie		Social Services Navigator
Brown, Victoria		Senior Manager Clinical Trials
Cardenas, Melissa		Nurse Practitioner, Specialty Care, Neurology
Choudhury, Parichita	MD	Physician - Dementia
Cline, Madison Paige		Senior Pathology Technician
Delgado, Jaztine		Associate Clinical Research Coordinator
Denkinger, Marisa	PhD	Staff Scientist
DePorte, Cynthia		Clinical Research Representative
De Santiago, Stephanie	DNP	Nurse Practitioner, Specialty Care, Neurology
Dhanani, Sara	MD	Physician, Movement Disorders
Dieckhoff, Kari		Pathology Research Technician, Biomarker Program
Evans, Brittani		Neuropsychology Assistant
Ghisays, Kathryn		Senior Clinical Research Program Manager
Glass, Michael		Psychometrist
Goddard, Molly		Senior Manager, Clinical Trials
Gulmen, Mine		Research Assistant
Gutierrez, Michele		Senior Manager, Clinical Trials
Hanley, Davron		Pathology Research Technician, Biomarker Program
Ho, Andrew	DO	Cognitive & Behavioral Neurologist
Intorcia, Anthony		Senior Manager, Pathology
Johnson, Michaela	NP	Nurse Practitioner, Specialty Care, Neurology
Krupp, Addison		Pathology Technician

Name (last, first)	Degree	Role on project
Kuramoto, Angela		Associate Director, Observational Research Cohorts and Clinical Trials
Liebsack, Carolyn	RN	Director, Clinical Trials
Liu, James		Biomarker Laboratory Operations Program Manager
Lohmeyer, Teresa		Manager, Research Administrative Services
Lorenzini, Ileana	PhD	Neuropathology Research Scientist
Lowery, Serena		Senior Research Recruitment & Outreach Manager
Mariner, Monica		Tissue Donation Coordinator
Marques, Taina	PhD	Senior Research Biomarker Program Manager
Martinez, Lupita		Clinical Research Representative
Mazo, Lennessa		Clinical Research Assistant
McHattie, Rylee		Pathology Technician
Moorefield, Paula		Business Support Assistant
Moorley, Naudia	PsyD	Psychometry Coordinator
Napierkowski, Madelynn		Clinical Research Representative
O'Connor, Kathleen		Clinical Research Coordinator
Oliver, Javon		Pathology Assistant
Orozco, Richard		Associate Clinical Research Coordinator
Qiji, Sanaria		Associate Manager, Pathology
Rangel, Amy		Clinical Research Lab Coordinator
Raymond, Lacey		Senior Psychometrist
Reade, Marina	DNP	Lead APP
Reyes, Priscilla		Psychometrist
Rosalez, Sirena		Psychometrist
Seifert, Jessie		Psychometrist
Serrano, Geidy	PhD	Director, Neuropathology Lab
Serrano Salcedo, Juan	PhD	Neuropsychologist
Shahub, Sarah	PhD	Post Doctoral Fellow, Biomarker Lab
Shaikh, Farah		Clinical Research Coordinator
Shprecher, David	DO	Movement Disorders Program Director, Neurologist
Shull, Anissa		Pathology Research Technician
Singh, Alpana	PhD	Postdoctoral Fellow
Souder, Alena		Psychometrist
Soza, Vanessa		Associate Clinical Research Coordinator
Surdyn, Michelle		Tissue Donation Support Navigator
Teran, Marlene		Associate Clinical Research Coordinator

Name (last, first)	Degree	Role on project
Trncic, Nadira		Clinical Research Program Manager
Valentino, Dayra		Nurse Practitioner, Specialty Care, Neurology
Walker, Jessica		Clinical Research Program Manager
Wermager, Zekiel		Pathology Technician

BARROW NEUROLOGICAL INSTITUTE
at St. Joseph's Hospital and Medical Center

Barrow Neurological Institute (BNI) at Dignity Health St. Joseph's Hospital and Medical Center is an international leader in the treatment, research and education of brain and spinal diseases, conditions, and injuries. BNI seeks to advance the knowledge and practice of medicine in neuroscience through basic and clinical research, education of medical professionals, and innovation in clinical techniques and technology.

The Alzheimer's and Memory Disorders Program at BNI, led by Anna D. Burke, MD, is committed to providing comprehensive clinical care and wraparound services for patients with memory disorders. In addition to clinical care, the program is committed to providing complementary support, education and outreach to Alzheimer's disease patients and caregivers.

In the past year, the program team has led: Care partner support groups for Alzheimer's disease (AD), frontotemporal degeneration (FTD), and Lewy body dementia (LBD). Memory Cafés, offered in both English and Spanish, that provide safe, stimulating activities for patients and respite for care partners. Dementia with Dignity virtual workshop series that provides care partners with information, practical tips, and support to overcome challenging aspects of providing care. Fall and Spring Care Partner Symposiums that allow care partners to learn from experts in the field about a variety of topics, including love languages, the impact of stress, how to embrace humor, and renewed hope during a time of challenge.

Under the leadership of Dr. Burke, program physicians Yonas Geda, MD, Marwan Sabbagh, MD, and Tom Finkelstein MD, also work closely with scientists and play an instrumental role in clinical and translational studies of AD and memory disorders. Research endeavors focus on prevention, early diagnosis, and treatment options for every stage disease. In 2025 and 2026, program clinicians led 22 active clinical trials and funding generously matched by the Institute's resources provides for support of pilot research project awards including development of novel imaging and cell based biomarkers for Alzheimer's and related dementias (ADRD) and various studies of new approaches to disease-modifying treatments, including monoclonal antibodies against pathological protein targets such as amyloid and p-tau, repurposing of existing drug therapies, agents reducing neuroinflammation, neuromodulation therapies, and lifestyle medicine interventions intended to improve cognitive function. Additionally, they conduct neuroimaging, biomarker, and observational trials to gain a greater understanding of the disease and to better tailor future therapies.

The close relationships between clinicians and scientists at BNI have propelled many cross-disciplinary studies currently underway and in development. Support from the Arizona Alzheimer's Consortium (AAC) has maintained the Hispanic Enrollment in Alzheimer's Research Trials (the HEART Program) focused on engaging underserved and understudied populations in clinical research, as well as establishment of the necessary infrastructure to engage, retain, and recruit Latinos.

In the past few years, neurodegenerative disease research at BNI has expanded with the addition of both accomplished senior faculty members and more junior investigators with promise and skill and new ideas about disease mechanisms and treatment opportunities. Laboratory and clinical resources devoted to this enterprise have also increased, and investment in faculty and resources is expected to continue and grow.

The Department of Translational Neuroscience at BNI is home to leading scientists and physician-scientists in neurodegenerative disease research, including Alzheimer's disease, Parkinson's disease,

amyotrophic lateral sclerosis (ALS), as well as neuroimaging, traumatic brain injury, cerebrovascular diseases, and stroke.

Robert Bowser, PhD, is Chief Scientific Officer and Chair of Translational Neuroscience for BNI. He is an internationally recognized leader in ALS research. His research at BNI is focused on discovery and validation of biomarkers for ALS and other neurodegenerative diseases. Additionally, his research explores the mechanisms underlying neurodegeneration, new technologies for the delivery of drugs into the central nervous system and defining the spatial expression of genes relative to neuropathology within human tissue samples. He has active funding from the Department of Defense (DoD) AL2000-61 on targeting chitinases as a novel therapy for ALS, NINDS funding (NS116385) to generate and characterize novel mutant MATR3 knock-in mouse models of disease; funding from Target ALS of over $1.5M per year for a post-mortem tissue banking program in ALS and a natural history study of ALS that collects longitudinal clinical measures, biofluids and at-home measures of speech and respiration; funding from the Chan Zuckerberg Initiative to expand diversity in ALS research and participation of patients in rural communities; and recently was awarded two additional DoD grants (AL220164 and AL220103) that total over $1.5M with Drs. Medina and Bakkar to study longitudinal neuroimaging and protein biomarkers in ALS patients as well as AAV mediated modulation of the retinoid pathway as a novel treatment for ALS.

Professor Elliott Mufson, PhD, is a pioneer in the application of single cell gene array technology to study the genetic signature of neurons during the progression of AD. Dr. Mufson's research focuses on the pathobiology of the normal and diseased human brain, including the neurobiology of mild cognitive impairment, which is a precursor to AD, Down syndrome, and traumatic brain injury. He is the head of a multicenter program project grant (P01AG14449) from the National Institute on Aging (NIA) entitled the "Neurobiology of Mild Cognitive Impairment in the Elderly" and principal investigator of a NIA grant (RO1AG061566) to investigate the genetic signature of tau neurons during the progression of AD.

Associate Professor Sylvia E. Perez, PhD, investigates the molecular mechanisms underlying neuropathology associated with cognitive decline and dementia in AD, Down syndrome, and traumatic brain injury and the preservation of cognitive functions in an exceptional population of very old individuals known as "Super Agers". Dr. Perez recently received funding from the NIH to examine the cellular and molecular changes associated with cognitive decline in Down syndrome (R01AG081286). This work aims to identify mechanistic pathways that may serve as therapeutic targets, laying out the foundation for the development of novel interventions with potential translational relevance to AD.

Assistant Professor David Medina, PhD, specializes in investigating neurodegenerative diseases including ALS, FTD, and AD, with a particular focus on identifying molecular mechanisms and therapeutic targets using cellular and mouse models. His work employs multidisciplinary approaches including multiomics, behavioral analysis, in vitro modeling, and therapeutic development strategies. He has received funding from the NIH/NINDS (R21NS116385) to develop novel mouse models of Matrin 3 gene mutations to identify mechanisms of ALS and FTD. Additionally, he is the primary investigator on a grant from the Arizona Alzheimer's Consortium to study shared mechanisms of neurodegeneration in AD and ALS, which supported preliminary studies leading to a recently awarded U.S. Department of Defense grant (AL250098) focused on targeting RNA modifications in ALS. His research also focuses on evaluating innovative therapeutic strategies, including small molecules, viral vector approaches, and gene-based therapies. Dr. Medina also serves as PI on a multiyear Therapeutic Idea Grant from the U.S. Department of Defense (AL2020-61), which supports the development of gene therapy approaches targeting retinoid signaling pathways for ALS and related neurodegenerative disorders.

Professor Rita Sattler, PhD, David and Weezie Reese Chair for Neurodegeneration Research, studies the role of synaptic biology in health and disease, particularly focused on understanding the role of synaptic dysfunction in neurodegenerative diseases such as FTD, ALS, AD and PD. Her lab employs

human patient-derived induced pluripotent stem cells (iPSC) and postmortem patient tissues, in addition to patient-derived biofluids (CSF, plasma) to elucidate the cellular and molecular mechanisms of neuronal cell death and the contribution of glial cells to neurodegeneration and synapse loss. Dr. Sattler is principal investigator and co-investigator of numerous active grants from the NIH/NINDS and the Department of Defense, as well as several disease foundations, including the Muscular Dystrophy Association (Glia-glia crosstalk), the Robert Packard Center for ALS Research (synaptogenic activity of astrocytes) and the Target ALS Foundation (role of TDP-43 in glial cells). This past year (2025-2026), NIH funding totaled over $1 million to Dr. Sattler and her team of investigators towards their research on the role of microglia and astrocytes in ALS and FTD (R01NS120331, R21NS141011) and the role of RNA processing in TDP-43 pathology (R01NS091299, 1R21NS130492), in addition to $700K from the Department of Defense on the mechanisms of synaptic protein dysfunction (AL200139). Finally, together with Multi-PIs Drs. Sabbagh, Criswell, and Racette, Dr. Sattler received a $10 million award (total) from Arizona State (GR-ARPA-BNF-050123-01) to study mechanisms of long COVID on neurological function and health outcomes.

The Barrow Neuroimaging Innovation Center was designed to advance imaging technology to improve patient diagnosis and care, serve as an imaging resource for the greater research community, and provide education in medical imaging. Ashley Stokes, PhD, associate professor of neuroimaging research, leads research that focuses on developing, validating, and translating advanced MRI acquisition and analysis methods to noninvasively assess neurological diseases and disorders, including AD, PD, and multiple sclerosis. Dr. Stokes aims to develop advanced imaging biomarkers that can inform on the underlying disease pathophysiology. She currently has funding from NIH to study imaging-related changes using advanced MRI methods in both PD and multiple sclerosis. Additionally, she received funding from the Arizona Biomedical Research Centre to assess neurovascular changes in aging and cognitively impaired populations.

Clinicians and scientists at BNI are also involved in training the next generation of researchers. Established in 2007, the ASU-Barrow Interdisciplinary Graduate Program in Neuroscience has been a collaborative effort between BNI, Arizona State University, the University of Arizona College of Medicine-Phoenix, and the Translational Genomics Research Institute (TGen), all of whom are members of the Arizona Alzheimer's Consortium. Led by Dr. Sattler, BNI faculty provide interdisciplinary research training and mentorship for students in areas such as ADRD, ALS, neuroimaging, PD, and stroke and vascular disease. Scientists also support and mentor undergraduate and high school students enrolled in BNI's summer internship programs. Students are provided with an opportunity to enhance knowledge of biological mechanisms that contribute to disease and learn how to use advanced scientific techniques to address scientific questions.

BARROW NEUROLOGICAL INSTITUTE
at St. Joseph's Hospital and Medical Center

Key Personnel

Name (last, first)	Degree	Role on project
Aliskevich, Emily	BS	Clinical Research Coordinator
Baez Cruz, Jessica	BS	Psychometrist
Boerhinger, Ashley	PhD	Neuroscientist
Beyene, Kassu	PhD	Biostatistician
Bowser, Robert	PhD	Chief Scientific Officer; Professor and Chair, Translational Neuroscience
Burke, Anna	MD	Geriatric Psychiatrist**;** Director, Alzheimer's and Memory Disorders Program
Chahal, Geetika	MBBS	Program Manager
Criswell, Susan	MD	Neurologist; CMO Barrow Neurological Institute
Eagan, Danielle	PhD	Neuropsychologist
Eudy, Victoria	MPH	Data Manager
Garcia, Angelica	BS	Project Manager
Gunning, Jordan	PhD	Post-doctoral Research Fellow
Hanson, Krista	PhD	Neuropsychologist
Hutson, Noah	PhD	Neuroscientist
Jensen, Kendall	PhD	Neuroscientist
Kanna, Latha	PhD	Biomarker Analyst
Kelly, Shannon	BS	Regulatory Manager
Khan, Nevine	MS	Project Manager
Killion, Jordan	PhD, MPH	Neuroscientist
Krzyzanowski, Brittany	PhD	Neuroscientist
Levy, Jennifer	BSc	Research Technician
McBride, Tori	RN	Research Nurse/ Study Coordinator
Medina, David	PhD	Neuroscientist; Assistant Professor, Translational Neuroscience
Perez, Sylvia	PhD	Neuroscientist; Associate Professor, Translational Neuroscience
Quezada, Giselle	BS	Research Technician
Sabbagh, Marwan	MD	Geriatric Neurologist; Vice Chair Research of Research
Sai, Shivani Chirag	MA	Analyst
Santiago, Jalisa	BS	Clinical Research Coordinator

Name (last, first)	Degree	Role on project
Sattler, Rita	PhD	Neuroscientist; Professor, Translational Neuroscience
Snell, Margeaux	MD	Program Manager
Spillman, Ashton	BSc	PhD Graduate Student
Racette, Susan	PhD	Neuroscientist
Williams, Stacy	MS	Biostatistician

CRITICAL PATH INSTITUTE

Critical Path Institute (C-Path) is a nonprofit, public-private partnership with the U.S. Food and Drug Administration (FDA) created under the auspices of the FDA's Critical Path Initiative program in 2005. C-Path's aim is to accelerate the pace and reduce the costs of medical product development through the creation of new data standards, measurement standards, and methods standards that aid in the scientific evaluation of the efficacy and safety of new therapies. These pre-competitive standards and approaches have been termed "drug development tools" (DDTs) by the FDA, which established a process for official review and confirmation of their validity for a given context of use. C-Path orchestrates the development of DDTs through an innovative, collaborative approach to the sharing of data and expertise. We build consensus among participating scientists from industry and academia with FDA participation and iterative feedback. The process, depending on the use case, culminates in a formal application to FDA for official "qualification" of the DDT for a given use in product development. Qualified DDTs then become open standards for the scientific community which, in turn, may be assured of the scientific rigor under which they were developed and of the FDA's understanding and acceptance of their validity.

The Critical Path for Alzheimer's Disease (CPAD) consortium accelerates drug development for patients with chronic neurodegenerative disease leading to dementia, primarily Alzheimer's disease. CPAD is collaborating with industry, regulators, and academia to leverage the wealth of drug development knowledge that the consortium members possess and enable pre-competitive widespread data sharing from clinical trials in AD. CPAD curates an aggregated database of anonymized patient-level data using CDISC consensus standards, from 89 different Phase II and III clinical trials and observational studies. The CPAD database is leveraged to develop various DDTs, such as model-informed disease progression models and clinical trial simulation tools that can be used for optimizing clinical trial design. CPAD is leading a precompetitive effort with leading academic and industry experts to 1) test and validate a tau-PET quantification method that harmonizes derived measures across different tracers and cohorts, and 2) explore and evaluate the readiness of tau-PET as a surrogate marker in AD drug development to support accelerated drug approval. Also, CPAD and the Alzheimer's Association's Global Alzheimer's Association Interactive Network (GAAIN) collaborate on establishing a neuroimage analysis framework, based on the Laboratory of Neuro Imaging (LONI) pipeline workflow, that is generalizable and reproducible, for use in clinical trials.

The CPAD database includes a rich variety of biomarker modalities (e.g., imaging, cerebrospinal fluid, blood) and longitudinal clinical endpoints, offering great potential for answering key questions in AD trial design related to screening, enrichment, and tracking disease progression. However, the complexity and diversity of CPAD's data pose a challenge for researchers more skilled in modeling than data processing. To address this, a user-friendly web-based interface called the "actionable data model" (ADM) tool has been developed to further enhance the utility of the CPAD database, facilitating data exploration, supporting model-informed drug development, and advancing research to increase the scientific understanding of Alzheimer's disease.

The CPAD-developed DDTs will drive the potential for scientific discovery and provide solutions to optimize the design of clinical trials of AD drugs intended for regulatory review in support of marketing approval.

CRITICAL PATH INSTITUTE

Key Personnel

Name (last, first)	Degree	Role on project
Karten, Yashmin	PhD, MPH	Scientific Director, Critical Path for Alzheimer's Disease
Jacobsen, Colleen		Project Manager, Critical Path for Alzheimer's Disease
Tatton, Nadine	PhD	Executive Director, Critical Path for Alzheimer's Disease
Stephenson, Diane	PhD	V.P. Neuroscience, Critical Path Institute
Henscheid, Nicholas	PhD	Scientific Director – Quantitative Modeling, Critical Path Institute
Ashton, Nicholas J.	PhD	Banner Sun Health Research Institute
Denkinger, Marisa	PhD	Banner Sun Health Research Institute

MAYO CLINIC ARIZONA

The main goal of this research program is to determine the correlation between genetic risk for Alzheimer's disease (apolipoprotein E [APOE] genotype) and the effect of normal aging on certain measures of cognitive function, brain volume, brain metabolism, cerebral amyloid deposition, and plasma biomarkers. It supports and extends our goals and efforts in our NIA funded Alzheimer's Disease Research Center. The principal institutions involved in this collaborative research effort are Mayo Clinic Arizona (primary site), Banner Alzheimer Institute, Barrow Neurological Institute, Arizona State University, The University of Arizona, and Translational Genomics Research Institute though as the program has matured, it has evolved into a core resource for investigators from these and other institutions as well. Our research program capitalizes on the clinical and neuropsychological expertise of the Behavioral Neurologists and Neuropsychologists at Mayo Clinic Arizona, in conjunction with the genetic expertise of Drs. Eric Klee and Rory Olsen of Mayo Clinic Rochester as well as Drs. Leonard Petrucelli and Matthew Baker at Mayo Clinic Florida. Through additional philanthropic support we have performed MRIs on more than 160 members and whole genome sequencing (WGS) on the 946 members of this cohort for whom we had stored DNA further fostering collaboration and extending our range of scientific inquiry. We plan to expand our MRI cohort with 7T MR in a subset. We also analyzed a large cohort of resilient agers through a collaboration with Drs. Owen Ross and Neill Graff-Radford from Mayo Clinic Florida, evaluating the impact of novel genetic risk factors on cognitive aging trajectories. Dr. Oana Dumitrascu continues develop her database of retinal changes of Alzheimer's disease (AD) in clinical and preclinical cohorts. Drs. Leslie Baxter and Bryan Woodruff serve as co-investigators for a multisite collaborative study with Dr. Blair Braden at Arizona State University evaluating aging outcomes in autistic adults. We plan to characterize the differences in polygenic risk scores for Alzheimer's disease and Autism in the autistic adult and APOE cohorts. Dr. Shannon Chiu expands our expertise in Lewy body disease with her NIH funded project evaluating novel MRI and EEG techniques to better understand neurodegeneration and neuronal fluctuations in dementia with Lewy bodies (DLB) and AD. Dr. Mary Ellen Koran applies her expertise in advanced metabolic and molecular imaging techniques to neurodegeneration and is working with our Transplant team to develop screening algorithms to identify undiagnosed neurodegenerative disease in transplant candidates with the goal of avoiding adverse transplant outcomes. Dr. Guarav Pradhan continues to refine the Oculo-Cognitive Addition Test (OCAT) as a practical, scalable quick cognitive screening assessment to identify individuals showing subtle cognitive decline.

Our longitudinal study design is a unique strength with our longest participants having been followed for 30 years. Cognitive and related behavioral data are analyzed with regard to demographic and health related factors (e.g., hypertension), APOE genetic status, physical and psychological stressors, cognition, and brain imaging measures. We have shown that neuropsychologically defined onset of Alzheimer's disease begins in APOE e4 carriers in their 50s which is confined to memory during the early preclinical phase and is associated with an increase in self-awareness of decline that is not mirrored by informant observation. In later stages of preclinical Alzheimer's disease, as patients get within a few years of incident MCI conversion, executive measures begin to decline and informant observations begin to parallel self-reports of decline. Finally, by the time MCI emerges, memory, executive skills, and in some cases visuospatial skills begin to decline; and subtle personality changes begin characterized by increased proneness to stress and reduced openness to new ideas and experiences. Missing from the preclinical profile is any indication of depression, but the development of personality changes lays the groundwork for behavioral manifestations which begin to emerge during the MCI stage.

In addition to our cognitive studies, we have created a biobank of plasma, serum, and DNA that has served as a core resource for collaborative members.

To date we have:

1. analyzed the longitudinal trajectories of all our measures, identified those showing significantly greater acceleration of decline in APOE e4 carriers relative to noncarriers, and developed a cognitive profile of APOE e4 driven pathological aging that defines the cognitive profile of preclinical Alzheimer's disease.
2. compared our incident cases of mild cognitive impairment (MCI) to a clinical (prevalent) group of matched patients to further define an early and late preclinical/early clinical phase in which we begin to see decline in non-memory measures, especially those sensitive to executive functions.
3. characterized the significance of subjective impairment as voiced by one's self as well as by one's informant and showed that both reflect an early stage of decline in a small subset, but that stress related symptoms overshadow the cognitive changes so that subjective impairment alone is an unreliable indicator of imminent decline.
4. showed that personality traits that increase one's proneness to stress further speed up age-related memory decline, and this effect is more apparent in APOE e4 carriers reflecting their inherent predilection for Alzheimer's disease. In contrast we found that the developmental sex-based cognitive advantages of women over men regarding verbal memory and men over women regarding visual memory do not buffer the rate of decline associated with APOE e4.
5. advanced a modification of the amyloid cascade hypothesis that shifts the role of amyloid from a gain of toxicity of the abeta peptide fragment to the loss of homeostasis and function of the APP system.
6. utilizing graph theoretical analytics of functional MRI data in cognitively normal carriers and non carriers of the APOE e4 allele, we identified that carriers showed a relationship between steepness of verbal memory decline and left hippocampal connectivity, in advance of hippocampal volume changes.
7. showed that in our cohort of older adults undergoing longitudinal assessment, we did not detect evidence for lingering adverse neuropsychological and behavioral effects following COVID 19 infection that was not severe enough to require ICU admission or prolonged hospitalization.
8. identified distinctive free-water MRI imaging changes in patients with DLB that was associated with clinical decline, representing an novel imaging tool to track progression.
9. characterized microglial and astrocytic activation in the APP/PS1 amyloid mouse model in response to aducanumab anti-amyloid immunotherapy, as well as the effects of discontinuing such therapy.
10. identified differences in performance on many neuropsychological measures in older American Indians compared with non-Hispanic Whites, even after controlling for demographic variables.
11. developed 2 distinct deep learning models trained exclusively on retinal color fundus photographs to classify Alzheimer's disease, demonstrating superior accuracy when compared to existing models.
12. adapted an evidence-based intervention (Program for the Education and Enrichment of Relational Skills) supporting social communication, peer interactions, independence, and interpersonal relationships to meet the needs of middle-aged and older autistic adults.
13. contributed to a pragmatic review of the clinical features, neuropsychological profiles, biomarkers and management approaches that differentiate prodromal dementia with Lewy bodies from prodromal Alzheimer's disease.

These types of analyses will continue well into the future permitting us to achieve our longer term goals of:

1. correlating changes in cognition and behavior with structure, metabolism, and pathology.
2. determining rates of symptomatic conversion from preclinical Alzheimer's disease to MCI, and from MCI to dementia.
3. developing a personalized predictive model based on genomic and other presymptomatic parameters for the timing of symptomatic conversion.
4. informing the design of primary and secondary prevention clinical trials.
5. providing a core resource to all our collaborative partners.
6. correlating nontraditional measures of neuropsychiatric status such as intellectual achievement, sleep patterns, and personality factors with presymptomatic cerebral amyloid levels.

7. determining the relative timecourse of change for emerging blood-based biomarkers that begin preclinically and may be helpful in determining not only biomarker status but time to symptomatic conversion.
8. contributing to the development of a personalized, inexpensive, and widely accessible diagnostic based on EEG through a deep learning approach in collaboration with an industry sponsor.
9. further characterizing the distinctive retinal perivascular amyloid plaque burden in subjects with normal and impaired cognition as an accessible, noninvasive diagnostic modality applicable across the AD continuum.
10. further characterizing the utility of the Oculo-Cognitive Addition Test (OCAT) as a screening tool to identify subtle cognitive decline and trigger more comprehensive evaluation in individuals at risk for developing mild cognitive impairment.

This research proposal has been peer reviewed and approved by the Mayo Clinic Institutional Review Board (IRB #259-99).

MAYO CLINIC ARIZONA

Key Personnel

Name (last, first)	Degree	Role on project
Baker, Matthew	BSc	Principal Research Technologist
Baxter, Leslie	PhD	Co-Investigator, Neuroimaging Scientist, Neuropsychologist
Brostrom, Deborah	BS	Clinical Research Coordinator
Caselli, Richard	MD	Co-Investigator, Behavioral Neurologist
Chiu, Shannon	MD	Co-Investigator, Movement Disorder Neurologist
Driver-Dunckley, Erika	PhD, MD	Co-Investigator, Movement Disorder Neurologist
Dumitrascu, Oana	MD	Co-Investigator, Cerebrovascular Neurologist, Neuro-ophthalmologist
Dumkrieger, Gina	MS	Principal Data Science Analyst
Ezenne-Nwoye, Adaeze	CNP, MSN, RN	Nurse Practitioner
Koran, Mary Ellen	PhD, MD	Co-Investigator, Nuclear Medicine Radiologist
Langlais, Blake	MS	Principal Biostatistician
Locke, Dona	PhD	Co-Investigator, Neuropsychologist
Mehta, Shyamal	PhD, MD	Co-Investigator, Movement Disorder Neurologist
Murphy, Jacqueline	CNP, DNP, FNP	Nurse Practitioner
Pelayo, Manuel	MBA, BS	Associate Clinical Research Coordinator
Pradhan, Guarav	PhD	Co-Investigator, Biomedical Informatician, Data Science Analyst
Roberts, Theodore	BA	Psychometrist
Saidi, Pouria	PhD, MS	Research Associate, Data Science Analyst
Stonnington, Cynthia	MD	Co-Investigator, Psychiatrist
Timm, Jordan	MA, BS	Associate Clinical Research Coordinator
Wicklund, Meredith	MD	Co-Investigator, Behavioral Neurologist
Woodruff, Bryan	MD	Principal Investigator, Behavioral Neurologist
Zhou, Yuxiang	PhD	Co-Investigator, Neuroimaging Scientist, Medical Physicist

MIDWESTERN UNIVERSITY

Midwestern University is a university of health sciences dedicated to the education of future health professionals. Midwestern has Colleges of Osteopathic Medicine, Graduate Studies, Optometry, Dental Medicine, Podiatry, Pharmacy, Veterinary Medicine, and Health Sciences. Within those Colleges are many additional programs including Nurse Anesthesia, Adult Gerontology Nurse Practitioner, Master of Science/Doctorate in Nursing Practice, Physician Assistant, Cardiovascular Sciences, Biomedical Sciences, various advanced nursing degrees, Occupational Therapy, Physical Therapy, Speech-Language Pathology, and Doctor of Psychology. Midwestern University also has several dual-degree programs including the Precision Medicine Program and a Master of Public Health program. We have multiple university-based clinics including the Multispecialty Clinic, the Eye Institute, the Dental Institute, and the Companion Animal Clinic. Midwestern has a rapidly growing and diverse research community focused on disease-specific research as well as basic science research. Our scientists and clinicians (for both human and veterinary patients) are involved in many different research efforts, with collaborations throughout Arizona and the U.S. Midwestern supports a broad range of research, from neurological disorders and cancer to infectious diseases and anatomical studies. The research environment at Midwestern is highly collaborative and designed to use the collective expertise of our colleagues to achieve common goals.

Multiple interdisciplinary research programs have been developed in the last few years and are thriving. The MWU Clinical Research Services (CRS) provides a comprehensive setting to conduct clinical trials, translational research and technology development regarding human and veterinary drugs, biologics, devices, nutritional products, and diagnostics. Midwestern has also developed the Nanomedicine Center of Excellence in Translational Cancer Research, with the goal of applying new technologies to the treatment of cancer. Midwestern also has an active Metabolism Center of Excellence to support research into metabolism and metabolic disorders. Our Veterinary Medicine program supports many diverse research programs which support the Midwestern University One Health Initiative, that focuses on bringing together both basic and clinical researchers from our various colleges to gain insights into the interrelationships between public health, biodiversity and sustainability. Our goal is to train our students in the interdependence of all healthcare professions, for the benefit of current and future patients.

To support the goals of the Arizona Alzheimer's Consortium, the faculty at Midwestern University have created a formal group, the Midwestern Alzheimer's Advisory Committee (MAAC), dedicated to research into Alzheimer's disease (AD) and related conditions. This group now includes faculty from 16 departments/programs and multiple colleges. Several new investigators interested in or already involved in AD research recently joined the university faculty and were added to the MAAC membership. The goals of MAAC are to 1) leverage this diversity of expertise and establish a common core of investigators that contribute to our understanding of neurodegenerative disorders and aging, 2) to inspire collaboration within Midwestern and with investigators at other institutions, and 3) to complement and enhance the efforts of other Consortium-affiliated institutions and investigators around the state. Future goals for Midwestern University's Consortium efforts include broader roles in basic science understanding, patient evaluation and treatment mechanisms, education and outreach, and clinical recruitment.

Current Alzheimer's research-related aims at Midwestern include:

1. Evaluating the potential role of microbes in the development of AD brain pathology and cognitive deficits. This research has involved studies of the microbiota, microbial components, and viruses present in post-mortem brain tissue from AD and MCI patients in comparison to normal and high

pathology non-demented controls. Most recently, subject brain tissue was assessed for the presence of fungi and fungal components. PBMCs from living subjects have been assessed as well to determine if microbes are likely to be entering the brain through the blood stream. In addition, mouse studies have included infection of 3xTG and APOE4 mice to test if infection with common microbes can exacerbate pathology in these models as well as a study evaluating gut microbiome changes in 3xTg and APOE3/4 mice.

2. Risk factors for AD include cardiovascular disease, type 2 diabetes, insulin resistance, and inflammation. The effects of various diets, exercise regimens and therapeutic compounds on the development of AD are being evaluated. High fat diets, high fructose/high sucrose diets, lean diets, and varying exercise regimens, as well as compounds like genistein and resveratrol, have been tested for their ability to induce or reverse AD pathology or cognitive decline. The brain-gut-bone and brain-muscle axes are being explored with the goal of understanding how risk factors are specifically linked to development of AD. In addition, the ability of exercise to reverse the negative effects of obesity on memory and neurocognitive function has been assessed. This is being done by determining the ability of exercise to modify the brain and intestinal metabolome of male mice fed high fat/high sucrose diets (HFHS) fed male mice and by assessing the ability of exercise to modify the phenotype and physical characteristics of HFHS fed female mice. Most recently, the brain and intestinal inflammatory states have been assessed to see if they are modified by HFHS diets or exercise.
3. Progranulin (PGRN) is a protein which shows functional alterations in transport and lysosomal processing early in the development of Alzheimer's pathology. We are conducting studies evaluating the role of progranulin in Alzheimer's disease. The goal of this work is to explore the lysosome-PGRN-inflammation axis in AD to determine whether therapeutic approaches aimed at lysosomal pH or PGRN restoration could prevent or reverse the neuroinflammation associated with AD. This work was extended by testing whether PGRN can reverse or inhibit the proinflammatory effect of IFN-gamma. Another central question investigated is the proposed causal link between inflammation and lysosomal processing of PGRN. Most recently, work is proceeding to understand the regulation of PGRN levels and the potential for boosting PGRN production in an effort to reduce neuroinflammation.
4. Applying the study of healthy aging to Alzheimer's disease by evaluating whether cellular senescence can be mitigated by intermittent fasting and its effects on metabolism, particularly insulin signaling. This study is being done in senescence-accelerated SAMP8 mice. In these mice, the role of age-associated inflammation in impaired insulin signaling and memory dysfunction can be explored. In addition, this study has examined exercise-induced mitigation of cellular senescence as a peripheral control mechanism for Alzheimer's disease. Enhanced ketone metabolism has been evaluated to assess if it can protect from age-related cognitive decline and to establish the effect of ketone bodies on the aging of peripheral tissues. Most recently, this project is studying cross-talk between the degenerating brain and peripheral tissues by characterizing the molecular and cell biology of peripheral tissues during the development and progression of AD using 5xFAD and APP/PS1 mice.
5. Exploring the role of the telomere-protecting RAP1 protein in the molecular steps leading to the development of Alzheimer's disease. Shortening of the telomeres is associated with cellular aging and increases with advancing age, which is the greatest risk factor for AD. This research includes 1) evaluating the ability of RAP1, recently identified as a gamma-secretase modulating protein, to affect APP cleavage (through interaction with presenilin 1 protein) and formation of amyloid peptides 2) further exploration of the ability of RAP1 to bind not only to telomeres but also to other binding sites within the genome and 3) evaluating a link between (RAP1) and a protein localized to astrocytes (GFAPδ), which also interacts with presenilin-1. This project studies the possibility

that GFAPδ variants will modulate the accumulation of amyloid deposits in a cell culture model and assesses the ability of RAP1 and GFAPδ to activate gamma-secretase. The relationship between oxidative stress and amyloid peptide production is also being explored, along with an attempt to identify RAP1 and TET3 target genes that may influence Aβ production. In addition, the mechanisms by which modulatory proteins alter gamma secretase are being examined.

6. The presence of obstructive sleep apnea (OSA) increases the risk of AD. This study seeks to understand how normal aging and OSA affect the control of upper airway tone as an initial step before investigating respiratory dysfunction links between OSA and AD. The effect of aging and chronic intermittent hypoxia on breathing modifications in young and aged mice is being evaluated. Additionally, postsynaptic excitatory muscarinic receptor expression and changes in cholinergic inputs to respiratory-related brain regions in response to aging and chronic intermittent hypoxia are being assessed.
7. Assessing the readiness of physical, occupational, and speech therapy practitioners to work with Alzheimer's disease patients as well as patients with related dementias. In addition, the effects of dementia on couplehood are being evaluated to assess how occupational therapists can best support couples in which one partner is experiencing dementia. This may improve the quality of life of both members of the couple. This work was recently expanded to include a well-structured study of the impact of art therapy for seniors in a homeless shelter who have indications of dementia and was also used to train healthcare students to better understand and care for this population.
8. A new series of studies on Kv6.1 silent subunit expression and function in hippocampal neurons during Alzheimer's disease were launched recently. Living patients and preclinical models have shown hippocampal neurons hyperexcitability as a common sign in the initial stages of AD. It is plausible to believe the hyperexcitability of these neurons is related to the symptoms of AD. The exact causative mechanisms of hyperexcitability are unknown, but ion channels certainly play a role in this regard. This study compares the hippocampus from 3xTg-AD mice with those from C57BL/6-129 mix (genetic background controls) mice in regard to: i) Kcng1 gene transcription levels, ii) Kv6.1 subunit total protein level, and iii) neuronal excitability and heteromeric Kv channel-mediated potassium currents.

MIDWESTERN UNIVERSITY

Key Personnel

Name (last, first)	Degree	Role on project
Jentarra, Garilyn	PhD	Administrative Principal Investigator
Al-Nakkash, Layla	PhD	Principal Investigator
Anderson, Sarah	MOT/OTR	MAAC Investigator
Ayala, Patrice	DPT	Co-Investigator
Babu, R.	PhD	Collaborator (Auburn University)
Bae, Nancy	PhD	Principal Investigator
Bussey, Kimberly	PhD	Principal Investigator
Bryant, Nelson	PhD	MAAC Investigator
Call, Gerald	PhD	MAAC Investigator
Caspers, Thomas	DDS	Principal Investigator
Castro, Monica	BS	Research Coordinator
Carvalho-de-Souza, Joao	DVM, PhD	Principal Investigator
Christensen, Stephanie	PhD	Co-Investigator
Chu, Ping	BS	Sr. Research Specialist
De la Montaigne, Alison	MOT	Co-Investigator
Eckman, Delrae	PhD	MAAC Investigator
Esfandiarei, Mitra	PhD	MAAC Investigator
Fitzgerald, Nancy	DDS	MAAC Investigator
Flint, Melissa	PsyD	MAAC Investigator
Frost, Jonathan	DDS	Principal Investigator
Gerber, Dawn	PharmD	MAAC Investigator
Gonzalez, Fernando	PhD	MAAC Investigator
Gu, Haiwei	PhD	Collaborator (ASU)
Haley, Nick	PhD	Principal Investigator
Halket, Christine	DDS	MAAC Investigator
Hernandez, Jose	PhD	MAAC Investigator
Huang, Vanthida	PharmD	MAAC Investigator
Hughes, Tiffany	PhD, MPH	Principle Investigator
Hull, Elizabeth	PhD	Principle Investigator
Jauregui, Estela	PhD	Principle Investigator
Jones, Carleton	PhD	MAAC Investigator

Name	Degree	Role on project
Jones, Douglas	PhD	MAAC Investigator
Jones, T. Bucky	PhD	Principal Investigator
Kaufman, Jason	PhD	MAAC Investigator
Korch, Shaleen	PhD	MAAC Investigator
Kozlowski, Michael	OD, PhD	MAAC Investigator
Lawson, Kathy	PhD	Principle Investigator
Lee, Keehoon	PhD	Collaborator (TGen)
Lewis, Kelsey	BS	Research Specialist
Leyva, Kathryn	PhD	Principle Investigator
Li, Weidang	PhD	MAAC Investigator
Olive, Foster	PhD	Collaborator (ASU)
Olsen, Mark	PhD	Principle Investigator
Menchola, Marisa	PhD, ABPP (CN)	Principle Investigator
Potter, Pamela	PhD	MAAC Investigator
Potter, Ross	PhD	Research Coordinator
Revill, Ann	PhD	Principal Investigator
Robinson, Catrina	PhD	MAAC Investigator
Rogers, Alexandra	BS	Sr. Research Specialist
Shim, Minsub	PhD	Principal Investigator
Storjohann, Tara	PharmD	MAAC Investigator
Swanson, Mark	PhD	Principal Investigator
Tullot, Tony	MD	MAAC Investigator
Turner, Tamara	EdD, OTR	MAAC Investigator
Vallejo-Elias, Johana	PhD	MAAC Investigator
Veltri, Charles	PhD	MAAC Investigator
Weissig, Volkmar	PhD	Principle Investigator
Whetzel, Alexis	BS	Research Specialist
Wickstead, Edward (Ted)	PhD	Principal Investigator

NORTHERN ARIZONA UNIVERSITY

Two units within Northern Arizona University receive funding from the Arizona Alzheimer's Consortium: The Pathogen and Microbiome Institute and the Departments of Social Work and Psychological Sciences within the College of Social and Behavioral Sciences. NAU ranks in the top 10 among all four-year, public institutions in Native American graduate student enrollment and in the top 100 of the National Science Foundation's research university ranking for research activity. The Pathogen and Microbiome Institute (PMI) is based at Northern Arizona University (NAU). The Center for Applied Microbiome Science at the Pathogen and Microbiome Institute has begun to engage in research on establishing a link between Alzheimer's Disease (AD) progression and the gut microbiota (the collection of microorganisms that inhabit an individual's gastrointestinal (GI) tract). To do this, we have established a colony of triple transgenic AD and corresponding wild-type mice for analysis of the GI microbiome and AD-associated pathology throughout the course of AD progression.

To accomplish our research goals, we leverage our AAALAC-certified animal facility, a state-of-the-art BSL-2+ laboratory, and a large capacity for sequencing and computing power to complete cutting edge studies of the microbiota in Alzheimer's disease. NAU hosts a high performance computing cluster ("Monsoon") that has all of the software needed for microbiome and transcriptome analyses installed, including the popular QIIME 2 microbiome bioinformatics platform (https://qiime2.org; developed by PI Caporaso's team of students and professional software engineers at PMI). The PMI at NAU has an in-house sequencing core comprised of an Illumina MiSeq, an Illumina NextSeq, and a MinION (Oxford Nanopore). The Sequencing Core provides easily accessible sequencing for all faculty and staff at PMI, by following specific systems for sample tracking, preparation, and output data transfer. The core also serves as a resource in the dissemination of novel methods and provides training for new staff in sample preparation.

The goals of our research in the AAC are to assess changes in microbiome composition in the gut and other body sites that correlate with AD disease progression. We hope that these studies will lead to microbiome-based interventions for AD that can be used to delay or prevent the onset of this devastating diagnosis. Secondarily, our studies will lead to a mechanistic understanding of the gut microbiome-brain axis in AD. In our current and future studies, we aim to establish a causative relationship between microbial community members and AD pathology and to translate findings from a preclinical murine model to human disease.

Our team in the Pathogen and Microbiome Institute at Northern Arizona University is well-positioned to achieve these goals. Dr. Cope has extensive experience with transcriptome analysis and host-microbiome interactions, and Dr. Caporaso is an expert in microbiome analysis, including recent work on using fecal microbiota transplant to improve behavioral symptoms of autism in a Phase 1 clinical trial. In addition to our laboratory and sequencing capacity, we are developing laboratory and bioinformatics best practices for microbiome research. This includes automated nucleic extraction methods, application and validation of the latest microbiome sequencing protocols, and development of QIIME 2 (led by PI Caporaso), a microbiome bioinformatics platform. A new feature implemented in QIIME2 is provenance replay, which will allow investigators to exactly reproduce an analysis performed in a published study. This was recently used in a pre-print resulting directly from AAC funds (https://doi.org/10.21203/rs.3.rs-1538737/v1), and is being prepared for publication. We are therefore uniquely positioned to advance knowledge of the relationship between the gut microbiota and AD. These goals are achieved through decentralized data provenance tracking wherein each step of the analysis is automatically recorded and easily obtained in the results.

Researchers in the College of Social and Behavioral Sciences at NAU are using Community-based Participatory Research (CBPR) methods to better understand the practical and emotional impacts of Mild Cognitive Impairment (MCI) on culturally-diverse individuals and families living in rural areas, as well as preferences for community-based delivery of supportive interventions. Our work is situated within the mild cognitive impairment (MCI) stage of the typical disease progression of Alzheimer's disease (AD), beginning with preclinical AD (i.e., no observable symptoms, but potential for changes in the brain), followed by MCI due to AD (i.e., mild impairments in objective performance across multiple domains), and ending in mild, moderate, and severe stages of Dementia due to AD. We focus our work with the AAC on individuals with MCI due to AD and their family caregivers because these individuals are at an elevated risk of transitioning to Dementia due to AD. Research on early detection and supports among individuals with MCI due to AD and their family caregivers is of paramount concern for maximizing effectiveness of clinical trials and efficiently using resources.

The long-term goal of our current and future studies is to develop accessible, culturally-informed, and scalable intervention technologies and resources to identify and support diverse rural families coping with MCI. We are partnering with senior and community centers throughout the Northern Arizona region, as well as the Hopi Tribe's Office of Aging & Adult Services, to determine preferences for identifying and monitoring symptoms of MCI, as well as for engaging in remotely-delivered supportive interventions. We also aim to identify essential components of a culturally-appropriate intervention by exploring rural families' experiences with MCI including how symptoms are expressed, their impact on daily life, instrumental, intrapersonal, and interpersonal problems to which they contribute, systemic barriers to accessing support, and practical advice for contending with symptoms, associated problems, and access barriers. Lastly, we aim to examine the impact of modifiable, multi-level (e.g., individual, dyadic, family, environmental) risk and protective factors on daily cognitive health among rural individuals with cognitive impairment and decline. We now have two pre-prints resulting directly from AAC funds that document our mixed-methods digital health protocol (https://doi.org/10.2196/preprints.77958) as well as findings from our qualitative arm of the study (https://doi.org/10.1101/2025.06.11.25329469).

NORTHERN ARIZONA UNIVERSITY – PMI

Key Personnel

Name (last, first)	Degree	Role on project
Barnes, Carol	PhD	Co-I
Barroso, Daisy	BS	Graduate Student
Caporaso, J Gregory	PhD	Co-PI
Chen, Yu Jung		Graduate Associate, Research
Conn, Kathryn	BS	Graduate Student
Cope, Emily	PhD	PI and Project Director
Dikshit, Shreya	BS	Graduate Student
Gothard, Katalin	MD, PhD	Co-I
Herman, Chloe	PhD	Software Engineer
Romero-Ortega, Mario	PhD	Co-I
Sterzinar, Christopher	MA	Lab Coordinator
Wagner, Dave	PhD	Executive Director, PMI
Wood, Colin	MS	Research Software Engineer

NORTHERN ARIZONA UNIVERSITY – SBS

Key Personnel

Name (last, first)	Degree	Role on project
McCarthy, Michael	PhD	Co-PI
McCoy, Megan	PhD	Co-PI
Cerino, Eric	PhD	Co-PI
German, Paulina	BA	Graduate Masters Student Researcher
Fleury, Katherine	MA	Graduate Masters Student Researcher
Shannon, Faith	PhD	Graduate Doctoral Student Researcher
Anh Duong, Duy	BSW	Graduate Masters Student Researcher
Johnson, Nizhoni	BS	Undergraduate Student Researcher
Tobias, Olivia	MA	Graduate Masters Student Researcher
Martinez, Margarita	MSW	Graduate Masters Student (Graduated)
Anderson, Travis	BSW	Graduate Masters Student (Graduated)
Horowitz, Chloe	MA	Graduate Masters Student (Graduated)
Taylor, Zachary	MA	Graduate Masters Student (Graduated)
Wicker, Alexandra	BS	Undergraduate Researcher (Graduated)
Seaton, Thomasina	MA	Graduate Masters Student (Graduated)
Black, Amanda	MA	Graduate Masters Student (Graduated)
Livingston, Raechel	MA	Graduate Masters Student (Graduated)
Dopson, Rasheera	MPH	Graduate PhD Student, NARBHA Scholar
Lucero, Louis	BS	Community Partner, Joe C Montoya Community and Senior Center, Coconino County
Lucero, Diana	BS	Caregiver Case Manager, Hopi Tribe's Office of Aging & Adult Services
Rodriguez, Vanessa	BS	Undergraduate Researcher (Graduated)
Seaton, Thomasina	MA	Graduate Masters Student (Graduated)
Gutierrez, Bianca	BS	Undergraduate Researcher (Graduated)
Shannon, Faith	MA	Graduate Masters Student (Graduated)
Cool, Kim		Community Partner, Bullhead City Senior Enrichment Center, Mohave County
Miller, Jimmy		Community Partner, Yarnell Regional Community Center, Yavapai County
McFadden, Kathy		Community Partner, Prescott Center on Rosser, Yavapai
Tsosie, Valerie		Community Partner, So' Tsho Foundation, Navajo County

Name (last, first)	Degree	Role on project
Walters, Joette		Community Partner, Tuba City Regional Health Care
Downing, Sam		Community Partner, CommonSpirit Health Prescott, AZ
Trembly, Faith		Community Partner, Silver Creek Senior Center, Navajo County
Fleury, Katherine		Undergraduate Researcher (Graduated)
Rasco, Fiona		Undergraduate Researcher (Graduated)
Andrews, Talitha		Undergraduate Researcher (Graduated)
Yellow, Kaylee		Undergraduate Researcher

TRANSLATIONAL GENOMICS RESEARCH INSTITUTE

The Translational Genomics Research Institute (TGen) is a nonprofit biomedical research institute dedicated to translating genomic discoveries into advances in human health. TGen's mission is to accelerate the application of cutting-edge genomic science to improve disease prevention, diagnosis, and treatment. By integrating basic research, clinical investigation, and emerging molecular technologies, TGen bridges the gap between laboratory discoveries and patient care, advancing innovative diagnostics and therapeutics across a broad range of human diseases. A defining strength of TGen is its extensive network of collaborations with academic institutions, healthcare systems, government agencies, and industry partners, all working together to accelerate the translation of scientific discoveries into clinical impact.

Alzheimer's disease (AD), Alzheimer's disease-related dementias (ADRD), and the biology of aging have been central areas of investigation at TGen since the institute's founding. Over the past two decades, TGen investigators have made numerous landmark contributions to the field, including: (1) conducting one of the first high-density genome-wide studies to identify common genetic risk factors for AD; (2) identifying key genetic determinants of episodic memory performance in cognitively healthy individuals; (3) leading one of the first large-scale studies to define cell type-specific gene expression differences between pathology-containing and pathology-free neurons in the brains of individuals with AD; (4) identifying protein kinase targets responsible for pathological tau phosphorylation and leveraging these discoveries to inform novel therapeutic strategies; (5) contributing to the development of a novel cognitive-enhancing therapeutic based on discoveries from human genetics; (6) identifying novel extracellular vesicle biomarkers in blood for AD diagnosis and disease monitoring; and (7) advancing specialized nano- and picobody-based therapeutics targeting molecular mechanisms underlying AD. These accomplishments have been made possible through longstanding collaborations with leading institutions, including Arizona State University, Banner Alzheimer's Institute, the University of Arizona, Banner Sun Health Research Institute, Barrow Neurological Institute, the National Institutes of Health, and numerous additional national and international partners.

Today, TGen maintains internationally recognized expertise in several complementary areas of AD and aging research. These include identifying rare genetic causes of AD through next-generation DNA sequencing; characterizing cell type-specific transcriptomic changes using laser capture microdissection, single-cell, and spatial genomic technologies; discovering fluid-based biomarkers through extracellular vesicle molecular profiling and other multi-omic approaches; and developing innovative therapeutic antibodies and drug candidates for cognitive enhancement and disease modification. TGen also serves as a genomics and biostatistics resource for the Arizona Alzheimer's Consortium, providing expertise in study design, molecular data generation, integrative genomic analyses, and interpretation of complex multi-omic datasets.

The overarching goal of TGen's Alzheimer's disease research program is to enable precision medicine approaches for neurodegenerative disease by identifying individuals at risk before the onset of clinical symptoms, discovering biomarkers that facilitate early detection and disease monitoring, uncovering novel therapeutic targets, and advancing a deeper understanding of the molecular mechanisms that drive disease initiation, progression, resilience, and healthy cognitive aging.

TRANSLATIONAL GENOMICS RESEARCH INSTITUTE

Key Personnel

Name (last, first)	Degree	Role on project
Ahearn, Mary Ellen	MS	Project Management
Alsop, Eric	PhD	Computational Scientist
Antone, Jerry	BS	Senior Research Associate
Balcerzak, Andrea	PhD	Postdoctoral Fellow
Barraza, Yareli	BS	Clinical Research Coordinator
Beres, Steven	BS	Research Associate II
Cadiz, Mika	PhD	Staff Scientist
Chambers, Darian	BA	Clinical Research Coordinator
DeBoth, Matthew	BS	Bioinformatician III
Ding, Zonghui	PhD	Staff Scientist
Ecca, Fabrizio	PhD	Staff Scientist
Fryer, John	PhD	Co-Investigator
Haug, Katelin	MS	Staff Scientist
Huentelman, Matt	PhD	Principal Investigator
Johnson, Megan	BS	Bioinformatician I
Kamzina, Aya	PhD	Postdoctoral Fellow
Lechuga, Cynthia	MBA	Manager, Grants & Contract & System Support Administrator
Mantri, Shivani	PhD	Research Associate II
Meechoovet, Bessie	MS, RN	Senior Research Associate
Metz, Danielle	BS	Clinical Research Coordinator
Moore, Bethine	BA	Clinical Research Coordinator
Mosqueda, Mario	BS	Research Associate II
Naymik, Marcus	MS	Bioinformatician III
Olney, Kimberly	PhD	Postdoctoral Fellow
Palomares, Dorothy	BS	Research Associate II
Piras, Ignazio	PhD	Co-Investigator
Price, Calla	BS	Clinical Research Coordinator
Robles, Laura	MBA	Project Accountant
Sloan, Jennifer	BS	Research Associate I
Song, Serena	MS	Bioinformatician I

Name (last, first)	Degree	Role on project
Taguinod, Francis	MS	Research Associate II
Tallant, Lauren	MS	Research Associate II
Van Keuren-Jensen, Kendall	PhD	Co-Investigator
Venkatachalam, Harshini	Sc.B	Bioinformatician
Ahearn, Mary Ellen	MS	Project Management
Alsop, Eric	PhD	Computational Scientist
Antone, Jerry	BS	Senior Research Associate
Balcerzak, Andrea	PhD	Postdoctoral Fellow
Barraza, Yareli	BS	Clinical Research Coordinator
Beres, Steven	BS	Research Associate II

UNIVERSITY OF ARIZONA

Researchers at the University of Arizona (UA) are engaged in a highly collaborative, multi-disciplinary program of research focused on advancing our understanding of the major risk factors for brain aging and age-related neurodegenerative disease, their underlying neural substrates, and ways to prevent, delay, or treat age-related cognitive impairment and dementia. Consistent with the mission of the Arizona Alzheimer's Consortium (AAC), our multidisciplinary strengths in cognitive neuroscience, clinical sciences, neuroimaging, and basic neuroscience uniquely position us for translational studies of both normative aging and pathological aging, including Alzheimer's disease. Investigators engaged in AAC research projects represent over fifteen departments and institutes in four colleges, encompassing the fields of neuroimaging, biomedical engineering, physics, neuroscience, cognitive neuroscience, neuropsychology, speech pathology, neurology, psychiatry, cardiology, surgery, pharmacology, physiology, electrical and computer engineering, optical sciences, and statistics. This program of research is strengthened by our close ties to other research units at UA including the **Evelyn F. McKnight Brain Institute**, focusing on understanding and preventing age-related memory impairment, and the **Center for Innovation in Brain Sciences,** focusing on the development of pharmacological interventions for neurodegenerative diseases. Additionally, our researchers are actively engaged in education and outreach in the Tucson community and across Arizona to enhance community outreach, education, and research participation by underserved minority groups in Arizona.

The AAC is strongly tied to the newly-established **BIO5 Brain & Body Imaging Center (BBIC)**. A major strength at UA is the development and utilization of novel imaging methods, most notably magnetic resonance imaging (MRI), as well as ultrasound imaging, positron emission tomography, and retinal tomographic imaging to measure brain structure and function in aging and age-related neurodegenerative disease, as well as methods for measuring neuronal activity and potential novel biomarkers in neural tissue. With funding from the AAC this year, BBIC further strengthened our ability to support the development and application of multi-modal imaging technologies while training the next generation of scientists. BBIC has also been instrumental in bringing together imaging experts across Arizona (see Progress Reports by Ryan et al. and Trouard et al.) to advance MRI methods, develop and implement novel image analysis pipelines, and encourage multi-site collaborative projects. These activities not only benefit researchers at UA but are also shared widely across the entire Arizona research community and beyond. We are committed to advancing the frontiers of imaging science, fostering innovation, and supporting researchers in their quest to improve quality of life and health. Our next-generation research-dedicated MRI scanners – the **Siemens Cima.X 3T**, the **Siemens Free.Max .5T** system optimized for whole body scanning, and the **Siemens Skyra 3T** system -- promise to significantly enhance multi-system studies of health and aging. In the coming year, we will build on our progress to date to further expand our ability to provide support to researchers at UA and across the State of Arizona engaging in imaging research.

The AAC at UA provides pilot grants to researchers engaged in innovative projects that include a range of scientific approaches from preclinical basic neuroscience to clinical interventions that translate across human and non-human animal studies of aging and disorders of aging. More than half (70%) of the projects utilize imaging modalities, including four projects on the development of novel MRI methods. UA's researchers engage in translational research that spans multiple areas of expertise and methods to address basic and clinical research questions concerning the factors that determine brain health and age-related brain pathology. These include investigating and tracking the neural systems and associated cognitive processes that are altered during the course aging and the development of age-related disease; evaluating how genetic, health, and lifestyle factors influence brain aging and cognitive decline; identifying novel biomarkers to improve early detection of brain changes due to aging and age-related diseases, understanding cellular mechanisms of brain aging in animal models; identifying and testing

novel interventions to improve cognitive functioning and decrease risk for AD, and developing novel methods for brain imaging and image analysis, most notably MRI.

The AAC pilot project program at UA continues to be extraordinarily successful. In 2025-2026, AAC researchers at UA held a currently-active extramural grant portfolio of more than **$233,240,000** from NIH, NIA, DOD, NSF, NHLBI, NIBIB, NIDA, NICHHD and NINDS, among others. More than **$122,600,000** in pending grants have also been submitted by this same group. A full list of these grants are provided later in this report. Many of these grants were supported by pilot data obtained through the AAC pilot project grant mechanism.

Details of each pilot project and their progress over the past year are included in the **Progress Reports** section below. Here, we provide an overview of programmatic activities at UA:

Novel image acquisition and analysis methods. We continue to develop novel MRI pulse sequences and pipelines for image analysis which, together with extensive raw imaging data, are made available to the research community through **OpenNeuro.org**, an NIH-funded online repository for neuroimaging data. Over the past year, AAC pilot funding was provided to create a novel AI-driven measure of brain aging (Bilgin); develop advanced diffusion MRI for measures microstructure and cerebrospinal fluid dynamics (Hutchinson); quantify in-vivo AD biomarkers such as ptau217 using advanced optical sensing technology (Su); and harmonize cross-vendor pulse sequences for pre-clinical and clinical multi-site studies (Chen, in collaboration with Mayo Clinic and Barrow Neurological Institute). These efforts are complimentary to the aims of the BBIC (Ryan, Trouard) in bringing together imaging experts across Arizona, sharing novel findings and methods, and encouraging multi-site collaborations.

Vascular contributions to aging and risk for AD. Our research team continues to focus on understanding the individual trajectories of normal aging and the early detection of cognitive impairments associated with aging, mild cognitive impairment (MCI), and Alzheimer's disease (AD). In the past year, multiple pilot projects focused on factors associated with vascular health, including determining how different aspects of physical activity relate to vascular brain measures and cognitive function (Alexander); investigating the impact of carotid disease on the integrity of the blood-brain barriers and age-related cognitive functioning in non-demented individuals (Arias); determining how the morphology of the vasculature as measured by retinal imaging relates to the presence of AD pathology (Pires); the role of glymphatic clearance in maintaining hippocampal integrity and optimal memory performance (Bartlett); the presence of pTau217 in patients with cardiovascular disease pre- and post-surgical intervention for carotid stenosis (Weinkauf); and the impact of micro-embolism in these patients related to cytokines present in cerebrospinal fluid (Zhou).

Neural mechanisms and biomarkers of age-related cognitive impairment and risk for AD. Researchers at UA are studying mechanisms of brain injury and neuroprotection, employing both human studies and non-human animal models, with the potential to identify targets for intervention and identify sensitive biomarkers that can be used to track brain changes associated with aging and age-related disease. This year, studies focused on understanding the relationships between the microbiome, vagal nerve activity, and brain health in a rodent model (Barnes); a comparison of technologies optimized for measuring neuronal spiking – a critical step in studies of NPTX2 resilience for synaptic functioning; and how neural ensembles in the hippocampus respond to novelty and motion (Cowen). Several studies focused on neuroinflammation, including the development of a novel assay for measuring neuron- and microglia-specific mitophagy (Rodgers); potential blockade of neuroinflammation (Gaffney); and the temporal association between ABeta deposition, neuroinflammation, and blood-brain barrier permeability (Shaik).

Potential interventions for cognitive impairment. Finally, several studies evaluated novel interventions or identified targets for interventions that may decrease risk for age-related cognitive impairment and/or AD. These included an evaluation of the potential positive impact of social interaction on neural flexibility and memory function (Grilli); combining TMS with phonological treatment to enhance clinical outcomes for individuals with Primary Progressive Aphasia (Kielar); and evaluating the impact of liver disease on brain health and cognition in Hispanic/Latino individuals utilizing MRI (Garcia).

UNIVERSITY OF ARIZONA

Key Personnel

Name (last, first)	Degree	Role on project
Aguinaga, Susan	PhD	Co-Investigator
Alexander, Gene	PhD	Principle Investigator, Director, Brain and Body Donation Program
Ally, Madeline	MA	Graduate Research Assistant
Altbach, Maria	PhD	Co-Investigator, MRI Physicist
Arias, Juan C	MD	Project Coordinator
Ashton, Nicholas	PhD	Co-Investigator
Baiocco, Laura	PhD student	Graduate Research Assistant, Psychology
Bartlett, Mitchell J.	PhD	Principal Investigator
Barnes, Carol A.	PhD	Principal Investigator, Director, Evelyn F. McKnight Brain Institute
Bayless, Karla	BS	Research Technician
Beeson, Pélagie	PhD	Professor, Co-Investigator, CCC-SLP
Beach, Thomas	MD, PhD	Director, Brain and Body Donation Program
Bedrick, Edward	PhD	Biostatistician
Bharadwaj, Pradyumna	PhD	Post Doctoral Fellow
Bilgin, Ali	PhD	Principal Investigator
Caporaso, Gregory	PhD	Professor, Department of Biological Sciences, NAU
Carlson, Rhea	BS	Graduate Student
Chen, Nan-kuei	PhD	Principal Investigator
Chen, Yu Jung		Graduate Associate, Research
Chou, Ying-hui	ScD	Principal Investigator
Cope, Emily	PhD	Assistant Professor, Department of Biological Sciences Assistant Director, Pathogen and Microbiome Institute NAU, Associate Professor, Biological Sciences
Cowen, Stephen L.	PhD	Principal Investigator
Das, Debottama	MS	Graduate Research Associate
Do, Loi	PhD	MRI Acquisition and Image Quality Control
Dolby, Aidan	BS	PhD student and collaborator
Dougherty, Russell	MA	Graduate Research Assistant
Doyle, Kristian P.	PhD	Collaborator
Echeverri, Jose	MD	Radiologist

Name (last, first)	Degree	Role on project
Escareno, Cristobal	BS	Clinical Research Coordinator
Espinoza, Mateo		Undergraduate Student
Felix, Mariana	MS	Clinical Research Coordinator III
Fotoohinasab, Atiyeh	PhD	Collaborator
French, Scott	BS	Blood-Based Biomarker Analysis
Gaffney, Kevin	PhD	Research Assistant Professor
Garcia, Alexis	BS	Project Coordinator
Garcia, Anozira		Research Coordinator
Garcia, David	PhD	Principal Investigator
Garner, Emma		Undergraduate Research Assistant
Gomez, Abigail		Undergraduate Research Assistant
Gothard, Katalin	MD, PhD	Professor, Physiology
Green, Jacob	MS	Project Coordinator
Grilli, Matthew	PhD	Principal Investigator, Associate Professor of Psychology
Haider, Nezam	PhD	Senior Research Scientist
Han, Silu	PhD	Collaborator
Hennessy, Sarah	PhD	Postdoctoral Scientist
Hovhannisyan, Mariam	MS, BA	PhD Student
Hsu, Chiu-Hsieh	PhD	Biostatistician
Huentelman, Matthew	PhD	Co-Investigator, Key Collaborator
Hutchinson, Elizabeth	PhD	Co-Investigator, Collaborator
Irwin, Kristina	BS	Research Manager
Jessup, Cortney	MPA	Research Coordinator
Johnson, Daniela	BA	Research Technician
Johnson, Kevin	BS	MRI Specialist
Jones, Eden		Undergraduate Student
Karakay, Deniz	MS	Graduate Research Associate
Katta, Sreeshanth		Undergraduate Research Assistant
Kiela, Pawel R.	PhD	Mentor
Kielar, Aneta	PhD	Principal Investigator, Department of Speech, Language and Hearing Sciences, Associate Professor
Lai, Vicky	PhD	Associate Professor, Collaborator, Psychology
Lehning, Ash		Undergraduate Student
Liang, Winnie	PhD	Administrative Director

Name (last, first)	Degree	Role on project
Lindemer, Shannon	MS	Co-Investigator/Senior Psychometrist
Liu, Yilin	PhD	Research Scientist
Lopez, Isabella	BS	Undergraduate Research Assistant, SLHS
Maldonado, Adriana	PhD	Co-Investigator
Markham, Donette	BS	Research Technician
Martin, Paige	MS	Graduate Research Assistant
Matijevic, Stephanie	PhD	Postdoctoral Fellow
Morrison, Helena	PhD	Collaborator
Mushtaq, Raza	MD	Neuroradiologist
Nelson, Isabella		Undergraduate Research Assistant
Nickels, Katlyn	PhD	Postdoctoral Fellow, Clinician, Speech-Language Pathologist
Ortiz, Olivia	MS	Graduate Research Assistant
Ozgur, Hasan	MD	Co-Investigator
Parmar, Raveena	BA	Graduate Assistant
Pederson, Vivianna	BS	Laboratory Technician
Pires, Paulo	PhD	Vascular Biologist, Collaborator
Rapcsak, Steven	MD	Co-Investigator, Physician, Professor, Neurology, UA and Banner Alzheimer's Institute
Rodriguez, Mariella	BS	Data Analyst
Rodgers, Kathleen	PhD	Principal Investigator, Associate Director, CIBS
Romero-Ortega, Mario	PhD	Department Head, Biomedical Engineering
Ryan, Lee	PhD	Principal Investigator, Brain & Body Imaging Center Director, Psychology
Savir-Baruch, Bital	MD	Principal Investigator
Serna, Mauricio	BS	Research Technician, Data collection, Data post-processing
Shaik, Shabana M.	PhD	Principal Investigator
Shankararaman, Dhana	PhD	Associate Scientist
Schmitt, Matt	PhD	Postdoctoral Fellow (replaced Asier Aristieta)
Sonderer, Christa	PhD	Collaborator
Srivathsa, Sahana	PhD	Postdoctoral Fellow
Sterzinar, Christopher	MA	Lab Coordinator
Stokes, Ashley	PhD	Collaborator
Su, Judith	PhD	PI, Director, Little Sensor Lab
Sun, Duohua	PhD	Collaborator

Name (last, first)	Degree	Role on project
Sundman, Mark	PhD	Research Scientist
Talapaneni, Mokshagna	MS	Data Analyst and programmer, Data Science
Toner, Brian	PhD	Co-Investigator
Trial, Michael	BS	Research Technician III
Trouard, Theodore	PhD	Principal Investigator, MRI Physicist
Vidana, Paola	BS	Clinical Research Coordinator
Vitali, Francesca	PhD	Bioinformatic Scientist
Weinkauf, Craig	MD, PhD	Principal Investigator, Co-Investigator
Wiskoski, Haley	BS, MS	Bioinformatics Analyst, Computational Image Analysis
Witte, Marlys	MD	Collaborator
Worley, Paul	PhD	Key Collaborator
Zahra, Summan	MD	Data Coordinator, Bioinformatics Analyst
Zempare, Marc	BS	Graduate Research Assistant
Zhang, Yichi	PhD	PhD student

UNIVERSITY OF ARIZONA - COLLEGE OF MEDICINE, PHOENIX

The University of Arizona - College of Medicine, Phoenix (UACOMP) is a rapidly growing medical school committed to excellence in education, biomedical discovery, and clinical care. Located on the Phoenix Biomedical Campus, UACOMP maintains a close partnership with Banner Health, one of the nation's largest nonprofit health systems, which enables the rapid translation of scientific discovery into improved patient outcomes. In recent years, UACOMP has prioritized the expansion of its research enterprise across basic, translational, and clinical domains, with increasing institutional investment directed toward neuroscience. As a part of this strategic effort, the new Department of Translational Neurosciences (TNS) was established in 2023, with Dr. James Bibb serving as inaugural Chair. TNS serves as a hub for interdisciplinary neuroscience research across the College, bringing together investigators, shared resources, and collaborative programs. Its mission is to advance research from mechanistic and pre-clinical discovery toward clinical applications. The department integrates molecular, cellular, circuit-level, and behavioral approaches to investigate brain function in health and disease, with brain aging and neurodegenerative disorders as areas of growing research strength.

Over the last few years, UACOMP has experienced substantial growth in the number of faculty with expertise and active research interests in Alzheimer's disease (AD) and related dementias. This growth spans multiple departments, including Translational Neurosciences, Basic Medical Sciences (BMS), Psychiatry, and Neurology, reflecting the college's growing commitment to interdisciplinary collaboration in AD, dementia, and brain-aging research. Recently recruited and existing faculty bring complementary expertise in molecular neuroscience, synaptic biology, behavioral neuroscience, neurogenetics, drug discovery, and bioinformatics. Together, this convergence of expertise has positioned UACOMP to pursue innovative AD and ADRD research supported by shared model systems and infrastructure across departments.

UACOMP investigators are advancing a multifaceted research program focused on disease mechanisms and the evaluation of novel therapeutic candidates for AD and related neurodegenerative conditions. Dr. Isabelle Schrauwen, in collaboration with Banner Sun Health Research Institute, is working on characterizing somatic mosaic variants in AD. Drs. Ayanabha Chakraborti and James Bibb are using proximity-labeling approaches to characterize synaptic protein-interaction networks and evaluating brain-penetrant kinase inhibitors for pro-cognitive efficacy in AD-relevant models. Dr. Shenfeng Qiu is investigating whether restoration of astrocyte-to-neuron signaling can improve synaptic function and reduce AD-related pathology. Dr. Ebenezer Yamoah is examining the mechanistic relationship between age-related hearing loss and AD, including its potential value as an early disease indicator. Dr. Zachary Taylor is investigating the role of piRNA-mediated transcriptional and epigenetic dysregulation in the comorbidity of depression and AD. Dr Camila de Avila is working on delineating the role of the brainstem nucleus incertus in brain aging and AD. These projects reflect UACOMP's broad, integrated approach to developing novel strategies for the early diagnosis and treatment of AD and ADRD.

This expanding research program is supported by a growing network of institutional core facilities, including the Neurocircuits and Behavior Core (NBC), Biomedical Imaging Core, and Flow Cytometry Core. Recent investments in super-resolution imaging systems, spectral flow cytometry instrumentation, spatial transcriptomics platforms, and other state-of-the-art research technologies have strengthened UACOMP's capacity to investigate the cellular and molecular processes underlying brain aging and neurodegenerative disease. The NBC complements these capabilities by supporting preclinical studies through standardized behavioral testing, translational touchscreen-based cognitive assessment, fiber photometry, and advanced two-photon miniscope system for longitudinal *in vivo* monitoring of neural activity in freely behaving animals. Together, these shared facilities provide an integrated platform for linking molecular and cellular pathology with circuit dysfunction, cognitive decline, and therapeutic response in brain aging, neurodegenerative disease, and related neurological disorders.

UACOMP's mission in AD-related research is substantially strengthened by its academic-clinical partnership with Banner Health. This collaboration enables discoveries emerging from UACOMP laboratories to be advanced through Banner Health's extensive clinical infrastructure and allows clinical observations and patient-derived questions arising within Banner's health system to inform the direction of preclinical and mechanistic research at the College. UACOMP faculty are increasingly engaged in joint planning of research initiatives, shared grant applications, and coordinated scientific initiatives with Banner-affiliated investigators, further integrating basic and clinical perspectives on AD and aging.

To build on this growing institutional commitment, to broaden engagement with the Arizona Alzheimer's Consortium (AAC), and to strengthen its contributions to AD research across Arizona, the UACOMP-AAC Chapter was established under the co-directorship of Drs. James Bibb and Ayman Fanous. The Chapter promotes AAC funding opportunities through a dedicated website and facilitates communication between UACOMP faculty and AAC partner institutions. It is also responsible for issuing calls for letters of interest for matched-funding opportunities and selecting the most competitive candidates through a structured peer-review process. For the 2026 funding cycle, the inaugural internal call received 18 applications from investigators across multiple departments, reflecting substantial interest in AD and brain aging research among UACOMP faculty.

Looking ahead, UACOMP is well positioned to expand its contributions to AD and ADRD research through continued faculty recruitment, strategic investment in shared research infrastructure, and stronger integration of basic, translational, and clinical programs. By fostering interdisciplinary collaboration and deepening partnerships with Banner Health and AAC member institutions across Arizona, the College aims to build a sustainable and nationally competitive program in Alzheimer's disease, related dementias, and brain aging. This integrated effort will support research spanning disease mechanisms, biomarker discovery, therapeutic development, and clinical translation while strengthening UACOMP's role in the statewide Alzheimer's research community.

UNIVERSITY OF ARIZONA - COLLEGE OF MEDICINE, PHOENIX

Key Personnel

Name (last, first)	Degree	Role on project
Acharya, Anu	MS	Research Scientist, TNS
Benoit, Deborah		Project Administrative Assistant
Bibb, James	PhD	Professor & Chair, TNS | Co-Director UACOMP-AAC Chapter
Chakraborti, Ayanabha	PhD	Assistant Research Professor, TNS | Principal Investigator
de Avila, Camila	PhD	Assistant Research Professor, TNS
Drake, John	PhD	Assistant Professor, Psychiatry
Fanous, Ayman	MD	Professor & Chair, Psychiatry | Co-Director UACOMP-AAC Chapter
Lee, Jeong Han	PhD	Associate Research Professor, TNS
Perez Flores, Cristina	PhD	Associate Research Professor, TNS
Qiu, Shenfeng	PhD	Professor, BMS | Principal Investigator
Schrauwen, Isabelle	PhD	Associate Professor, TNS | Principal Investigator
Shin, Jisook		Research Professional, TNS
Taylor, Zachary	PhD	Assistant Research Professor, Psychiatry | Principal Investigator
Valenzuela, Itzi Adane	BS	Research Technician, TNS
Vladimirov, Vladimir	MD, PhD	Professor, Psychiatry
Yamoah, Ebenezer	PhD	Professor, TNS | Principal Investigator
Zafar, Talal	PhD	Postdoctoral Fellow, TNS



PROJECT PROGRESS REPORTS

ARIZONA STATE UNIVERSITY
PROJECT PROGRESS REPORTS

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Using AD tissue & organoids to study metabolic dysregulation in degeneration. Madeline Andrews, PhD, David Brafman, PhD, Haiwei Gu, PhD. Arizona State University; Arizona Alzheimer's Consortium.

Specific Aims:

Aim 1: Functionally measure & perturb metabolism in cortical cells during degeneration.
Hypothesis: Decreased astrocyte glycolysis impairs neuronal respiration leading to death.
1.1: Validate identified gene expression changes in AD patient tissue & degenerating organoids.
1.2: Define temporal changes in cellular metabolomes during aging & degeneration using LC-MS.
1.3: Perturb identified signaling changes & evaluate metabolic & degeneration consequences.

Aim 2: Evaluate how APOE4 affects metabolism & degeneration onset in patient iPSCs.
Hypothesis: Genetic drivers of AD will increase degeneration rate & discrete metabolic changes.
2.1: Identify molecular features of disease and correspondence to AD patient data.
2.2: Temporally quantify metabolic changes from patient-derived organoids.
2.3: Target patient-specific metabolic programs and measure impact on degeneration onset.

Background and Significance:

Alzheimer's Disease (AD) is the most common neurodegenerative disease with one of the highest rates of drug development failure (>99%)[1,2]. The lack of successful therapies corresponds to the limited understanding of AD pathophysiology and the dynamic factors that contribute to disease onset. Omics studies of post-mortem AD brain tissue have greatly improved the resolution of molecular changes indicating differences in core metabolic programs in AD patient neurons and astrocytes; these cells regulate cortical function and have tight metabolic exchange[3–5]. In AD, changes in metabolism are age-associated, linked with impaired neuronal activity, and may affect degeneration susceptibility [6–8]. Glucose hypometabolism is an early event in AD that may precede the onset of clinical symptoms [6,7]. Impaired glucose uptake by astrocytes may originate from decreased sensitivity to insulin/IGF1, thus decreasing metabolic support for neurons and impacting susceptibility to pathological changes. Previous studies provide essential molecular insights into end-stage disease; however, we **must identify early drivers of degeneration onset and progression to define potential therapeutic targets**. Human induced pluripotent stem cell (iPSC)-derived models, like organoids, serve as robust cellular platforms to study the relevant human cortical cell types vulnerable to disease. Organoids can be leveraged to temporally investigate and functionally perturb factors that contribute to AD pathology, particularly in disease onset, that cannot be obtained from post-mortem tissue. Although rodent models have many advantages, aspects of human neurobiology and degeneration are not well reflected. Due to complex human cell type composition, organoids can be used to investigate the role of neuron and astrocyte pathologies in AD and identify how changes in metabolic programs may contribute to disease onset and progression. Moreover, functional metabolic measures can be novelly, tractably employed to investigate bioenergetic changes in degenerating human astrocytes and neurons, to determine programs implicated in driving-disease pathology. Toward this goal, we will leverage AD patient samples and robust features of control and *APOE4* patient-derived organoids to evaluate relationship between metabolic changes and onset of cortical degeneration.

Proposed One-Year and Long-Term Outcomes:

One-year outcomes: We will evaluate the metabolic programs that are altered during degeneration onset sporadically across aging (Aim 1) and in patient *APOE4* lines (Aim 2). We will validate changes in AD patient tissue and organoids. We will functionally characterize bioenergetics of cortical cells during degeneration onset. We anticipate glucose uptake and lactate production will decrease around 5

months, due to decreased astrocyte glycolysis, with a subsequent decrease in pyruvate/citrate in neurons. Metabolic perturbations of insulin and glucagon signaling may rescue metabolic impairment and delay degeneration onset. We anticipate more rapid/altered degeneration onset in *APOE4* lines. These studies will allow us to disentangle genetic vs sporadic/environmental drivers of degeneration and bioenergetic changes in vulnerable cortical cell types. Studies will be submitted for publication and used as preliminary data for NIH application.

Long-term outcomes: We will mine our omics datasets for temporal biomarkers of degeneration onset and identify novel therapeutic targets, as metabolism is highly druggable. Proposed studies use novel approaches and advanced human models to identify patient phenotypes to functionally interrogate the relationship between metabolic and genetic drivers of neurodegeneration onset.

Year End Progress Summary:

Aim 1: Functionally measure & perturb metabolism in cortical cells during degeneration.

1.1: Validate identified gene expression changes in AD patient tissue & degenerating organoids. We analyzed sc-RNA-seq data from prefrontal cortices of patients with Alzheimer's Disease (AD) and control individuals and compared to 1-year forebrain organoids, observing overlap with cell types from AD patients. We observed decreased abundance of glycolysis genes in AD patient astrocytes, including insulin receptor (INSR, IGFR1) and glucose transporters (GLUT1). We probed indicators of biological activity via functional enrichment, which corroborated changes in metabolism-regulating pathways between AD patients and aged organoids. Astrocytes shared increase in insulin and glucagon signaling, while neurons had changes in metabolically targeted pathways, like mTOR and HIF1-a.

To interrogate the temporal regulation and onset of degeneration-associated changes in organoids over time, we collected a timecourse of aging organoids for sc-RNA-seq at early, pre-degeneration periods (1-3 months), during onset of features (5-9), and after extensive neuron death (9-11 months). Organoids have been collected, sequenced, and processed for quality control, batch correction, and clustering/annotation. We are currently analyzing combined datasets (organoids vs primary dataset benchmarking) to assess molecular changes in cell types during degeneration onset using differential gene expression analysis. Concurrently, we developed metabolic gene signature networks of discrete pathway activity and are applying to distinct subtypes of neurons and glia. This large dataset is considerably expanded in scope compared to originally planned experiments, requiring more complex, computationally intensive data wrangling, processing, analysis and computing resources. Thus far, our temporal, comparative analysis findings indicate that insulin resistance in astrocytes may impact changes in glucose uptake and glycolytic production of lactate, which fuels neurons, and in turn may impair neuronal energy production. The coalescence of metabolic programs and regulated pathways indicate a dysregulation in metabolism in disease-relevant human cortical cell types, which may drive degeneration onset. To test this data-driven hypothesis, we have validated degeneration features in 1 – 11 months in six different iPSC lines and observed onset of pTau accumulation and metabolic dysregulation between 5-7 months, concurrent with onset of astrocyte reactivity. Subsequently, we observe neuron death between 9-11 months, during which astrocyte hypometabolism occurs. Different subpopulations of neurons have distinct vulnerability to cell death, with inhibitory interneurons and superficial lamina cortical excitatory neurons being particularly vulnerable. Additionally, while glycolytic indicators are highly expressed early, they decline dramatically over time, confirming glucose metabolism dysregulation observations from single cell analysis.

To molecularly validate changes from organoids, we have been working with Drs. Geidy Serrano and Ileana Lorenzini through the *Banner Body and Brain donation bank* to acquire prefrontal cortex tissue samples from AD individuals and age-matched controls. We validated protocol efficacy for fluorescent *in situ* hybridization (FISH) in patient brain tissue. This validation required significant post-processing and protocol optimization. We are currently assessing observed dysregulated metabolic pathways in

organoids in AD patient samples and age/sex-matched controls focusing on changes in insulin, glycolysis, and glucagon-regulating genes in astrocytes and hypoxia and mTOR genes in neurons.

1.2: Define temporal changes in cellular metabolomes during aging & degeneration using LC-MS. While sc-RNA-seq is a powerful approach to assess cell type-specific gene expression changes and facilitates post-mortem patient molecular analysis, RNAs are not equivalent to metabolites.

Changes in metabolic pathways require functional measurement; direct metabolite measurement is necessary to identify changes in homeostasis. While metabolomic approaches are incompatible with post-mortem analysis, aged organoids are an ideal system to measure and quantify functional changes over time, facilitating insights into degeneration onset. Organoids were differentiated from five iPSC lines for 11 months and collected every other month (from 3-11 months) for LC-MS metabolomics. Polar metabolites were extracted using methanol-isolation and lyophilization. To assess temporal metabolic changes, in collaboration with Dr. Haiwei Gu, we measured metabolites across the aging timeline we defined in Aim 1.1. The isolation of metabolites, sample processing, and analysis required significant optimization, as this is an entirely novel approach. However, these data are yielding exciting, potentially transformative understanding of energetic changes across cell types and biomarkers that may indicate degeneration onset. Initial analyses confirm that glycolytic metabolites are highly abundant at early periods (1-3 months) and transition to TCA/OXPHOS subsequently during neuron and astrocyte maturation periods (3-5 months). Glycolytic metabolites/lactate, that would be anticipated in mature astrocytes, were not observed at peak maturation periods (5-7 months), similar to RNA-seq results. Additionally, while ‘aged’ 9–11-month organoids have the greatest abundance of neurotransmitters (ACh, GABA, L-tyrosine) expected of mature neurons, redox regulators of oxidative stress, L-cysteine/glutathione, and nicotinamide that produces electron carrier, NAD, are also highly abundant at this timepoint. These data provide functional evidence of metabolic dysregulation that supports transcriptomic observations in tissue and organoids.

1.3: Perturb identified signaling changes & evaluate metabolic & degeneration consequences. For metabolic perturbations, we pivoted from strictly targeting identified pathways with drug/signaling perturbations to also change nutrient access, via glucose concentration in media. We are currently analyzing changes in low-glucose cultured organoids vs standard (hyperglycemic) conditions of aged organoids to assess improvement/prevention of degeneration features. We have now cultured organoids for five months and observe decreases in ROS and increased production of upper layer cortical neuron subtypes that were vulnerable to cell death in Aim 1.2. Preliminary analyses suggest improved neuron health and delayed cell death. Next, we will explore impact, prevention, or delay of astrocyte reactivity phenotypes and neuronal accumulation of pTau.

Aim 2: Evaluate how APOE4 affects metabolism & degeneration onset in patient iPSCs. Through collaboration with Dr. David Brafman, we acquired two APOE4 AD lines with paired isogenic controls (corrected to APOE3) and multiple clones of each line to investigate metabolic contribution and temporal onset of degeneration features in aging organoids. We expanded and differentiated APOE lines. However, given differences in expansion/maintenance substrate (Cultrex vs Matrigel), we had complications with adherence and spontaneous differences with several clones delaying initiation of Aim 2 studies. However, one clone per individual has been successfully expanded for the full differentiation time course, while other lines are currently in organoid culture at earlier timepoints. We are currently processing organoids to assess phenotypic observation of timing of neuronal abundance/health, accumulation of pathological indicators (pTau, B-amyloid), and death, as well as any changes to astrocyte reactivity/state. Given observations regarding dysregulation of glucose metabolism in control lines, which provides insight into potential environmental mechanisms of sporadic disease, we are processing organoids for metabolic measures and will begin culturing under

physiologic levels of glucose.

Progress toward long-term goals: Data from this study was submitted for R21 (impact score: 44) and R01 (22%) proposals that received scores but were not funded. One manuscript is under review/revision with *Cell Reports* and a second is being compiled for preparation to submit in Winter 2026 to *Nature Neuroscience*. Additional data with perturbations and APOE4 lines are being compiled for a NIH R01 submission in Fall 2026.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Characterizing the effects of a clinically-used SERM menopausal hormone therapy on cognition and hippocampal plasticity. Heather Bimonte-Nelson, PhD, Juliana Kling, MD, MPH. Arizona State University; Arizona Alzheimer's Consortium; Mayo Clinic Alix School of Medicine.

Specific Aims:
The specific aim of this project is to determine the impact of the clinically-used SERM Bazedoxifene across varied loads of learning and memory demands and for hippocampal plasticity.

Background and Significance:
Bazedoxifene (BZA) is a selective estrogen receptor modulator (SERM) given to menopausal women in combination with conjugated equine estrogens (CEE), providing a tissue-selective estrogen complex. The SERM BZA has enhanced selectivity relative to other SERMs, and is clinically used as a CEE+BZA combination. Clinical and preclinical research show that CEE+BZA can antagonize estrogens' effects on the uterus, yields no or minimal uterine stimulation, and in menopausal women who have a uterus, treatment obviates the need for a concurrent progestogen (NAMS, 2017). A therapy that obviates the need for a progestogen is desirable. For example, we and others have shown in rats that many progestins negatively impact cognition and reverse cognitive-enhancing E2 effects (Bimonte-Nelson et al., 2004, 2006; Koebele et al., 2022; Braden et al., 2010, 2011, 2015, 2017; Prakapenka et al., 2018). The 2022 Menopause Society Hormone Therapy Position Statement highlights that women with an intact uterus taking systemic estrogen should receive a progestogen, unless they are taking CEE combined with BZA (NAMS, 2022), underscoring the utility of this novel therapy and the need to decipher its comprehensive effects. In healthy menopausal women, CEE+BZA improved vasomotor symptoms, bone density, sleep, and lipid profiles (Mirkin & Komm, 2013). Of note, while there is limited BZA-alone work done on the CNS, one preclinical study showed that BZA enhances remyelination (Rankin et al., 2019). *We have an exciting opportunity* to leverage our established rat models to systematically test the effects of BZA alone and in combination with CEE for neurobehavioral effects. We will test each component alone and combined in the ovarian hormone blank-slate, previously established, Ovx rat model. This study will fill a critical knowledge gap regarding whether this novel therapy prescribed to uterus-intact menopausal women, unique in that it does not contain a progestogen, extends benefits to cognition when given during middle age. We hypothesize that CEE will improve spatial cognition in middle-age rats given our prior findings (Acosta et al., 2009, 2010; Engler-Chiurazzi et al., 2011; Hiroi et al., 2016), and that BZA will not reverse these benefits.

Preliminary Data:
We have established the parameters of CEE effects for spatial working and reference memory, showing that in middle-aged Ovx rats, several CEE doses enhanced spatial working memory, overnight memory retention, prevented scopolamine-induced impairment, and increased ChAT+ basal forebrain neuron counts (Acosta et al., 2009, 2010; Engler-Chiurazzi et al., 2011). Here, we use these CEE administration parameters as a positive control, and as a baseline for which to add BZA in combination, as given in the dual CEE+BZA menopausal hormone therapy.

Proposed One-Year and Long-Term Outcomes:
By the end of the one-year project period, rats will be ordered, and surgeries and behavior testing will be completed. We will score, analyze, and write the data into manuscript form immediately after this time period. To follow, we will perform brain assessments to correlate with behavioral cognitive data. Regarding long-term outcomes, expected deliverables include a

manuscript submitted within about 18 months from study initiation, and the data will be included in a preclinical menopausal hormone therapy grant to NIH. In all, our outcomes will take a systems approach to further understand menopause and hormone therapy effects on brain function during aging, with a particular focus towards optimizing brain and overall health outcomes for women across the lifespan.

Year End Progress Summary:

As proposed, rats were ordered immediately and surgeries were initiated. Rodent learning and memory testing has been completed. We are in the process of scoring the behavioral data and are analyzing final results. We are also planning to perform brain assessments of plasticity markers to correlate with memory. Regarding long-term outcomes of grant proposals and publications, we expect that the data will be completely collected and analyzed for a publication over the next year, and a grant proposal to study broader effects of this combination therapy on memory, the brain, and hormone systems across menopause variations.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Determining the mechanisms of the protective effective of the Reelin-COLBOS variant. David A. Brafman, PhD, Thomas G. Beach, MD, PhD, Geidy Serrano, PhD, Bryan Woodruff, MD. Arizona State University; Banner Sun Health Research Institute; Mayo Clinic; Arizona Alzheimer's Consortium.

Specific Aims:

Genome-wide association studies (GWAS) have identified numerous genetic variants that increase the risk of sporadic Alzheimer's disease (AD), guiding most therapeutic efforts toward risk mitigation. However, protective variants offer an alternative avenue for prevention-focused interventions. A recently identified rare variant in RELN (H3447R), termed RELN-COLBOS, was associated with delayed neurodegeneration in a PSEN1 mutation carrier, suggesting its potential as a protective modifier of AD. To study the molecular mechanisms underlying this effect, we will use human induced pluripotent stem cell (hiPSC) lines derived from well-characterized post-mortem brain donors (Banner Sun Health Research Institute) and AD research cohorts (Mayo Clinic). These lines provide a powerful model system that complements animal studies. To eliminate variability from genetic background, we will apply our high-efficiency gene editing approach to generate isogenic hiPSC lines with and without the RELN-COLBOS variant. We will differentiate these lines into neuronal (glutamatergic and GABAergic), astrocytic, and microglial populations to investigate the impact of RELN-COLBOS on AD-related phenotypes and molecular processes. We hypothesize that RELN-COLBOS confers protection through modulation of Aβ dynamics, tau phosphorylation, and transcriptional regulation, and that these effects may be cell-autonomous or non-autonomous.

Aim 1: Introduce the RELN-COLBOS variant into isogenic hiPSC lines using TREE-based genome editing. We will edit hiPSC lines from non-demented controls and AD patients to introduce the RELN-COLBOS variant and perform rigorous quality control to confirm genomic integrity, pluripotency, and tri-lineage differentiation capacity.

Aim 2: Determine the functional impact of RELN-COLBOS on AD-related cellular phenotypes and molecular pathways. Differentiated cell types will be analyzed to assess the variant's effect on Aβ processing and uptake, tau phosphorylation, and transcriptional changes. We will also evaluate whether RELN-COLBOS confers protection via cell-intrinsic or extrinsic mechanisms.

Overall, this project will provide critical insight into how RELN-COLBOS modifies AD risk, informing future therapeutic strategies focused on enhancing neuroprotection.

Background and Significance:

Reelin (RELN) is an extracellular glycoprotein critical for neurodevelopment and adult brain function, influencing processes such as cell migration, dendritic branching, synaptic plasticity, and the balance of neuronal excitation and inhibition. Predominantly secreted by GABAergic interneurons, RELN signals through canonical pathways involving VLDLR/ApoER2 receptors and DAB1 phosphorylation, activating downstream cascades that regulate cytoskeletal stability and neuronal homeostasis. In Alzheimer's disease (AD), RELN expression is reduced, contributing to impaired synaptic function and increased tau phosphorylation. While elevated RELN levels have been shown to reverse AD-related phenotypes, the underlying mechanisms remain unclear. Of particular interest is the recently identified RELN-COLBOS variant (H3447R), found in a PSEN1 mutation carrier, which appears to confer neuroprotection potentially through enhanced DAB1

signaling. Understanding how RELN-COLBOS mitigates neurodegeneration could reveal novel therapeutic strategies for AD prevention and treatment.

Preliminary Data, Experimental Design and Methods:

Generation of hiPSC-based cortical cultures. We have developed and optimized robust protocols for the large-scale generation of hiPSC-derived neurons, astrocytes, and microglia, including subtype-specific populations such as excitatory glutamatergic and inhibitory GABAergic neurons. These neuronal populations express mature and subtype-specific markers and demonstrate functional activity, including calcium transients consistent with their roles. Importantly, GABAergic neurons show high levels of RELN secretion, while astrocytes express APOE and actively take up Aβ. We have also established tri-culture systems with defined cellular ratios, enabling controlled and reproducible modeling of complex brain microenvironments[62]. Our ability to generate pure populations of neurons, astrocytes, and microglia that can also be dissociated and re-cultured in defined ratios provides a unique ability for control and reproducibility.

Highly efficient generation of isogenic hiPSC lines. Using our transient reporters of editing enrichment (TREE) editing platforms, we achieve high-efficiency (≥80–90%) single base-pair genome editing in hiPSCs with minimal off-target effects. These methods enable rapid generation of isogenic lines that differ only at specific loci, such as AD-associated variants. Prime-induced nucleotide editing using a transient reporter for editing enrichment (PINE-TREE) uses a fluorescent reporter system to enrich for successfully edited cells, allowing for both precise point mutations and gene knockouts. This approach provides a powerful toolset for generating RELN-COLBOS isogenic hiPSCs for mechanistic studies.

Using hiPSCs to investigate how genetic factors modulate AD risk. We have developed and applied isogenic hiPSC models to investigate how both common and rare genetic variants influence Alzheimer's disease (AD) risk. Using our TREE-based genome editing platform, we introduced these variants into hiPSCs from non-demented control and AD patient backgrounds to study their effects in a controlled genetic context. For example, our recent studies examining common APOE isoform, uncovered mechanisms by which various isoforms increase[64,65] or decrease[66] AD risk by perturbing Aβ accumulation and tau phosphorylation, with astrocytes playing a key role in mediating these risk-modifying effects. Most recently, we modeled the rare APOE Christchurch variant and confirmed its reported protective effects on tau pathology, demonstrating our ability to faithfully replicate resilience-associated phenotypes. Overall, these experiments demonstrate our ability to use isogenic hiPSC lines to investigate the mechanisms by which RELN-COLBOS modulates AD risk.

Proposed One-Year and Long-Term Outcomes:

Overall, this resource-generating, hypothesis-testing, and hypothesis-generating proposal will provide insights into the risk-modifying effects associated with variation in the RELN gene. As such, the data obtained as part of this proposal will set the stage for future hypothesis-testing studies to probe the mechanisms by which RELN-COLBOS enhances neuroprotection against AD. Such investigations will have a significant impact on the design of molecularly targeted therapies to treat AD. Although the proposed studies will not interrogate all of the hypothesized mechanisms by which APOE and biological sex interact to impact AD risk, we will uncover clues that will set the stage for future more detailed studies to apply for more comprehensive grants to funding agencies (e.g. NIH, Alzheimer's Association, American Federation for Aging Research, Brightfocus Foundation) to further mechanistically probe these links. Publication and presentation

of results shall occur during the project, if appropriate, or at the end of the project, consistent with normal scientific practices. The Brafman laboratory has previously received AAC funds which led to the generation of preliminary used in several successful grant applications to the Alzheimer's Association, Department of Defense, and National Institutes of Health. In fact, the last time we received AAC funds in 2023-2024 led to the generation of preliminary data which was used in a grant that was funded by the NIH (R21AG085395).

Year End Progress Summary:

We have made substantial progress toward the goals of this project, particularly with respect to the generation of the cellular models needed to study the protective RELN-COLBOS variant in a controlled human genetic background. In Aim 1, we successfully generated isogenic human induced pluripotent stem cell (hiPSC) lines carrying the RELN-COLBOS variant using our TREE-based genome editing approach. These edited lines have been characterized to confirm successful introduction of the variant and to evaluate overall cell quality, including maintenance of hiPSC morphology and pluripotency-associated features. Establishing these isogenic hiPSC models is a major milestone for the project because it allows us to directly compare cells with and without the RELN-COLBOS variant while minimizing variability due to differences in genetic background.

We are now advancing Aim 2 by differentiating these RELN-COLBOS isogenic hiPSC lines into disease-relevant neural cell types. Current efforts are focused on generating glutamatergic and GABAergic neurons, which will allow us to assess how the RELN-COLBOS variant influences neuronal phenotypes that are relevant to Alzheimer's disease. These differentiations are ongoing, and we are beginning to conduct AD-related phenotypic assays to evaluate the effects of RELN-COLBOS on cellular processes linked to disease pathogenesis, including Aβ-related phenotypes, tau phosphorylation and neuronal vulnerability. These studies will help determine whether RELN-COLBOS alters AD-associated cellular pathways in a manner consistent with a protective effect.

In parallel with these experimental milestones, we have leveraged the progress from this project to support a new NIH R21 application focused on protective genetic mechanisms in Alzheimer's disease. This application was recently reviewed and received a score in the 2nd percentile, providing strong external validation of the significance and promise of this research direction. Together, the generation and characterization of the RELN-COLBOS hiPSC lines, ongoing neuronal differentiation studies, initiation of AD-related phenotype assays and successful R21 review outcome demonstrate strong progress toward the overall goal of defining how RELN-COLBOS modifies AD risk and identifying protective pathways that may inform future therapeutic strategies.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Arizona Alzheimer's Consortium Public Conference. David W. Coon, PhD. Arizona State University; Arizona Alzheimer's Consortium.

Specific Aims:
a) Host the Arizona Alzheimer's Consortium Public Conference.
b) Collaborate across institutional partners to help identify speakers and market the conference to the public.
c) Collect data to gather demographic characteristics of the attendees and evaluate conference participant perceptions of benefit derived from attending the conference. Results will be used to enhance future public conferences sponsored by the AAC and its partners.

Background and Significance:
In 2025, over 7 million Americans were living with Alzheimer's disease (AD). With the aging of our society, the US percentage of persons age 65 and older with AD is expected to grow to 13 million by 2050. Nearly 12 million Americans provide unpaid care for people with Alzheimer's or other dementias. This care takes its toll on the physical health and emotional well-being of family caregivers. The non-match funds will be used to host the Arizona Alzheimer's Consortium's (AAC) statewide public conference targeting diverse groups of older adults facing cognitive decline including ADRD, their family caregivers, their providers, and other interested members of the public. Dr. David W. Coon will oversee all aspects of the project including identification of the venue, speakers, and panelists as well as the development, distribution, and analyses gather from the conference's evaluation tool gathering demographic characteristics of the attendees and their perceptions of benefit derived from their attendance. Findings will be shared with AAC leadership and staff to enhance future public conferences.

Year-End Progress Summary:
The AAC Public Conference was held in person at Arizona State University's Health Futures Center in North Phoenix on Saturday April 11, 2026 (8:15 a.m. to 1:00 p.m.). Based on public feedback from prior conferences, a Saturday was chosen to allow those who work during the week to attend and bring other family members. The conference planning committee built off of the suggestions of representatives from Banner Alzheimer's Institute Family and Community Services, AZDHS, AZDES-DAAS, AARP, Barrow Neurological Institute, and the Desert Southwest Chapter of the Alzheimer's Association. The program provided substantive but relatively short talks of 15 to 20 minutes delivered by experts in ADRD, new drug treatments for ADRD, prevention of ADRD, strategies for keeping your brain health, care planning interventions for people with living alone with cognitive decline, and the results from a recent caregiving intervention trial for family caregivers who have placed their loved ones with ADRD into long term care facilities. The day ended with performances by Shine Your Light Choir (a welcoming choir for people living with memory loss and those who care about them) followed by a panel discussion with expert providers from healthcare and community services including BAI Family and Community Services, Mayo Clinic Arizona, AARP, and the Alzheimer's Association.

This year's AAC Public Conference was similar to other free conferences where registration (well over 400 registrants and last minute walk-ins) was much higher than those that ended up attending in person (close to 300 attendees). The conference drew a record number of exhibitors who reported that the conference provided valuable and ongoing streams of useful interactions with attendees.

The majority of people who completed the post-conference survey self-identified as women (79%), college graduates (69%), and non-Hispanic White (78%). The largest ethnic/racial minority self-reported as Hispanic/Latino (8.2%) followed by Asian (6.6%), Black/African American (3.3%), Native

American/American Indian/Alaskan Native (3.3%). Ages ranged from 16 to 88 years of age (average age = 67.8 years old). Slightly less than half (47%) had attended the AAC Public Conference before, with only 26% reporting that they had participated in a research study about AD or aging and memory decline by AAC, the Arizona ADRC, or one of its partners. These findings indicate the conference reached beyond the AAC's network to a new audience and provided the opportunity to engage these attendees in research projects.

Most of the participants heard about the conference through email directly from the AAC (43.8%), a relative or friend (21.9%), employer or colleague (12.5%); health or social services provider (12.5%); an email from a healthcare or other community-based organization (10.9%); or social media posts (6.3%). The remainder reported learning of the conference from our websites, the research study staff, or flyers. Over 100% were overall satisfied by the conference, would recommend it to others, learned something they could use, and thought the conference met their expectations; 99% thought registering for the conference was simple.

Almost all of those completing the survey (98.3%) stated they were able to better understand the progress being made in Arizona regarding the early detection tracking and treatment or prevention of ADRD.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

CarePRO Virtual DS/ID (Down Syndrome/Intellectual Disabilities): Pilot Study of a Video-Conference Intervention. David W. Coon, PhD, Abigail Gomez Morales, PhD, RN, Anna Burke, MD. Arizona State University; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Specific Aims:

a) Conduct a single arm pre-post study using the CarePRO Virtual DS/ID intervention via Zoom with up to 20 participants through a pilot feasibility and acceptability trial.
b) Conduct appropriate statistical analyses to characterize the sample, examine the feasibility and acceptability of the intervention, and describe the impact of the intervention on key outcomes.

Background and Significance:

An underserved and understudied group of family caregivers impacted by Alzheimer's Disease and related dementias (ADRD) are those who assist adults with Down syndrome (DS) or another Intellectual Disability (ID) who also develop ADRD as they age. ADRD is the leading cause of death of people with Down Syndrome (approximately 70%). Recent research estimates clinical symptoms appear after the age of 40 (mean age of diagnosis is 55) with close to 50% developing Alzheimer's by age 60, and prevalence reaching 75-80% of the population older than age 60.[1-3] Lifelong caregiving, amplified by the onset of ADRD, may create "double jeopardy" for informal caregivers helping people with DS/ID. Moreover, no evidence-based interventions have been identified to help these family members and friends manage changes in their loved one's care, caregiving associated stressors, and caregiver-related distress.[4,5]

Recent meta-analyses and reviews of caregiver intervention research show that several approaches (e.g., psychoeducation skill-building, cognitive behavioral psychotherapy, and multicomponent interventions) are effective in enhancing positive mental outcomes, yet few if any have been adapted and effectively translated for those caring for this population.[6,7] Moreover, COVID-19 heightened the need for new modes of delivery to enhance accessibility of evidence-based caregiver programs for family caregivers for people with ADRD.[8,9]

Preliminary Data, Experimental Design, and Methods:

CarePRO Virtual DS/ID, the caregiver intervention investigated in this proposal, addresses a key gap in the literature by incorporating approaches that enhance the original CarePRO evidence-based psychoeducational skill-building intervention[10-12] and expand its reach to caregivers of people with DS/ID and ADRD. It does so via Zoom-delivered interactive group sessions for caregivers that provide proven skill-building strategies through trained co-leaders in a group setting that also help reduce social isolation. Zoom-delivery has the potential to reach family caregivers who are often left out of caregiver interventions due to their work schedules, geographic residence (e.g., rural caregivers), and other barriers (e.g., homebound due to their own health concerns, transportation challenges, or lack of respite options).[12] During Zoom-based coach calls, CarePRO Virtual DS/ID enhances the opportunity for caregivers to engage in home practice activities that have been shown to reinforce skill development and that have been found to be associated with better short-term and longer-term outcomes.[12-13] As part of our US Administration for Community Living (US ACL) project, we conducted a pre-pilot with six family caregivers of people with DS/ID and dementia with positive results. The methods for the current project included the following:

a) Implement an establish screening, interview, and intervention protocol for video-conference (Zoom) delivery of CarePRO Virtual DS/ID based on prior data from: (1) focus groups with family members and providers who assist this population; (2) evaluations from DS/ID and caregiving educational workshops conducted with community partners (Alzheimer's Association, Desert Southwest Chapter and local community based organizations serving older adults and people with disabilities); and (3) pre-pilot examination of the intervention with six family caregivers as part of the US ACL pilot project.
b) Collaborate with Dr. Anna Burke and her staff at Barrow Neurological Institute (BNI) to help recruit this hard-to-reach population of family caregivers, given BNI's expertise with this population and national connections.
c) Conduct a single arm pre-post study using the CarePRO Virtual DS/ID intervention via Zoom with up to 20 participants through a pilot feasibility and acceptability trial.
d) Use appropriate statistical analyses to provide descriptives that characterize the sample and further examine the feasibility and acceptability as well as inferences to describe the impact of the intervention on key outcomes.
e) Disseminate findings through presentations at national conferences such as the Gerontological Society of America and the National Down Syndrome Advocacy Conference.

Proposed One-Year and Long-Term Outcomes:

The proposed short-term outcomes are described in the Methods section. In addition, the data analyses would yield both professional presentations at meetings like the Gerontological Society of America, the American Society on Aging, National Down Syndrome Advocacy Conference, or American Psychological Association as well as the submission of the pilot results to venues like *The Gerontologist (Practice Concepts Section), the Clinical Gerontologist,* or *Dementia*. Subsequently, the PIs would submit either an R21 or an R01 or other nationally competitive proposal in 2027 depending on the pilot project's findings.

Year End Progress Summary:

Recruitment for caregivers of people with DS/ID who are developing dementia as they age proved to be much more challenging than anticipated. Our prior work through the US ACL project showed high interest from families caring for loved ones with DS/ID as well as the providers who serve these families. People showing interest in the project were often concerned about the future of their loved one who wasn't yet experiencing decline rather than those who had loved ones already experiencing changes in memory or behavior due to Alzheimer's or another dementia. As a result staff needed to spend much more time in outreach and following up through personal contact to well over 70+ individuals across 50+ organizations, including strong national and local organizations such as the National Down Syndrome Society, LuMind IDSC Foundation, the Global Down Syndrome Foundation, Advocate Medical Group, DSNetwork Arizona, DS-Connect Registry, National DS Congress, the National Task Group on Intellectual Disabilities and Dementia Practices, and the Arizona Developmental Disabilities Planning Council. Through these connections we also reached out via social media, listings through their online newsletters, and presentations (e.g., presentation to the Facebook group "Aging with Down Syndrome" that has 1,000 followers). We established strong connections for future collaborations in this area of research with several organizations interested in future grant collaborations. While analyses are still in process, 100% of participants reported: overall benefit from CarePRO DS/ID, better understanding of memory loss and its effects on people with DS/ID; felt more confident in dealing with their loved ones problems; made their lives easier; enhanced their ability to care for their loved ones; and helped improved their loved ones lives. Participants also reported improvement in their overall mood; positive aspects associated with caregiving; social support from others; amount of time in leisure activities; caregiving confidence; future care preparation; communication

with their loved with DS/ID and with others. After completion of analyses, we plan to collaborate with one or more of our national partners on the submission of an R21 or other appropriate mechanisms to further test CarePRO DS/ID.

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ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Arizona Alzheimer's Consortium Website Updates. David W. Coon, PhD, Jessica Langbaum, PhD. Arizona State University; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Project Description:

These project funds will be used for ongoing development and enhancement of the Arizona Alzheimer's Consortium's (AAC) website and increase its interoperability, accessibility, and information sharing activities to help launch new and sustain existing Alzheimer's disease (AD) research opportunities and findings advanced by the AAC across Arizona and beyond. Ongoing enhancements help to underscore the AAC as home to the nation's leading model of a statewide collaboration in AD research. As an umbrella organization, the AAC also encompasses the Arizona Alzheimer's Disease Research Center (ADRC) sponsored by the National Institute on Aging. Key project activities include website maintenance (e.g., platform hosting and security, data tracking), video publishing, tech support; media and video content for websites and social media distribution, video "vlogs" with scientists, edits of existing and production of new campaign material for distribution in English and Spanish. This approach helps our brand build trustworthiness and security as well as connect and engage with our audiences. Strong AAC branding demonstrates to the state and our communities that all our member institutions under the AAC and ADRC umbrella are united in their efforts to end Alzheimer's disease. This enhanced brand package continues to be incorporated into both websites azalz.org and azadrc.org and funnels participants, the general public, and scientists to our overall outreach efforts. These funds help support ongoing updates to the AAC website to maintain the latest website standards (including security standards).

Year-End Progress Summary:

The team continues to advance the AAC Website through enhancements of website operations for the AAC and its collaborative activities with the Arizona Alzheimer's Disease Research Center (ADRC) which includes the AAC member institutions and their scientists. These advancements required the following: ongoing refreshes to branding and design guidelines across web and video/print media to accommodate refinements based on technology and platform / user experience updates (backend database functions, web security, and multi-platform optimization); rollout of a tagline to crystallize our efforts for the public; continued deployment of our new logo honoring the wide variety of individuals and families impacted by ADRD, heritage, history, outreach, and our extremely broad and deep scientific platform; integrating the logo and tagline with both the AAC and ADRC for comprehensive branding across all media and by all users (member institutions, contractors/vendors, media outlets, social media, etc.); continuing web development work, such as usability, platform, and scalability testing to ensure the sites work on common browsers and devices (desktop, laptop, and mobile); improving contact and data intake methods for the public to express interest in participating in research studies and AAC conferences; fostering interoperability between the AAC and the ADRC websites; liaising with AAC Communications Committee members and institutional subject matter experts to review (and edit as needed) new original content and to help source additional content; curating and updating a Vimeo social media channel with more than 25 hours of existing content related to key categories (Alzheimer's Treatment and Management, Brain Health and Alzheimer's Prevention, Caregiving, and Conversations with Our Scientists) embedded into the websites; sourcing images to reinforce AAC, ADRC, and member institution commitments to reach across the diversity of our state and its communities; circulating content on a non-public staging server for review before public-facing publish testing including "platform breaking" to ensure performance and that the site is publication-ready.

Video content on the AAC and AZADRC platforms continue to achieve thousands of impressions. There is ongoing review of additional content that is to be published to the websites in the next year including up-to-date presentations from our scientists; more than new graphics and images sourced for use; and

new video footage of our communities to emphasize the far-reaching effect of our multi-site statewide presence. This year our scientists and researchers delivered informative presentations at our 2026 AAC Public conference with close to 300 in-person attendees and which was recorded and will be distributed through our online video channels. Video footage and interviews from the upcoming 2026 AAC Scientific Conference will be published as well.

Key website content has been translated from English to Spanish (and in some cases is produced in Spanish and translated to English) to continue reach populations at higher risk for Alzheimer's disease and related dementias (ADRD) including the Latino/Hispanic community. Content is also developed and made available for repurpose into additional social media and traditional media campaigns.

Ongoing services include ongoing work with AAC member institutions to source additional video content and develop new original content; the development of fresh, dynamic, bilingual material that will meet the informational needs of our communities, including populations at higher risk for ADRD such as the Latino and Native American communities; ongoing art direction and graphic design that strengthens branding between the AAC and the ADRC sites and our member institutions, and enhances community engagement; and collaboration with additional contractors/vendors to distribute content into target markets. Content will continue to be developed and refreshed in future years—making this not a one-off effort, but instead a substantial and ongoing push to expand public engagement, publicize research opportunities, and deepen institutional collaboration and connections.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Outreach, Recruitment, and Ongoing Engagement of Research Participants. David W. Coon, PhD, Jessica Langbaum, PhD, Geidy Serrano, PhD, Alireza Atri, MD, Anna Burke, MD, Bryan Woodruff, MD. Banner Alzheimer's Institute; Mayo Clinic Arizona; Banner Sun Health Research Institute; Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.

Project Description:

This proposal requests complementary support to enhance ongoing efforts for participant recruitment and outreach efforts as part of the Arizona Alzheimer's Consortium's ADC and ancillary programs with a particular focus on Latino and Native American Communities. The Arizona ADC is part of a multi-institutional state-wide consortium that links together the major research institutions in Arizona to advance effort in the early detection, tracking of progression, and evaluation treatments and prevention therapies for Alzheimer's disease and related disorders. The ancillary programs include the Arizona BBDP and Arizona APOE4 Gene Dose Program. The Arizona Brain and Body Donation Program (BBDP) provides an invaluable scientific resource of longitudinal cognitive, motor, clinical, and genetic data from >800 living older adults who have standardized annual assessments, consent to brain (and frequently body) donation, and provide a resource of unusually high-quality brain tissue, postmortem CSF and blood samples (which differ in some respects to samples that are acquired in life) and neuropathological data after they die. The program includes but is not limited to research participants with the clinical features of Alzheimer's disease (AD) or related disorders and cognitively and neurologically unimpaired older adults with support from the National Institute on Aging (NIA)-supported Arizona ADRC Center (ADRC), research participants with the clinical features of Parkinson's disease (PD) and related disorders and cognitively and neurologically unimpaired older adults with support from the National Institute of Neurological Disorders (NINDS)-supported National Brain and Tissue Resource for PD and Related Disorders (NBTR-PD). The Arizona APOE4 Gene Dose Program provides an invaluable scientific resource of longitudinal data from initially cognitively unimpaired research participants with two, one and no copies of the APOE4 allele, the major genetic risk factor for AD. The program includes over 200 participants who were initially late-middle-aged participants with a first-degree family history of dementia who are followed every two years with a battery of clinical ratings, cognitive tests, FDG, amyloid and now tau PET scans, and MRIs, who have provided plasma, serum and PBMC samples that are stored at Mayo Clinic, and who have begun to provide CSF samples with support from a longstanding NIA grant. It also includes more than 200 other participants, with or without a family history and through youngest to oldest adult ages, who are followed using state and organizational Arizona Alzheimer's Consortium funds, and who have not yet provided CSF, plasma and serum samples.

Latino and Native American Recruitment, Enrollment: The inclusion of Latino and Native American participants from a variety of backgrounds and different characteristics (e.g., level of educational attainment, race, country of origin, family history of AD) will assist investigators in providing answers to questions about dementia diagnosis, treatment, and management strategies that are likely to be applicable to the broad U.S. population. Additionally, a more diverse participant pool will facilitate investigations of different risk factors, health disparities and the neuropathology and genetics of AD and related dementias as well as studies of caregiving and family burden in diverse groups. As part of increasing outreach to families facing cognitive decline, this project advances our media/marketing campaign in both English and Spanish. The campaign

is set up to include events as well as print, video, social media assets and local TV material. It expands the marketing campaign and related assets that leverage traditional media (e.g., radio, TV, and print) and social media venues to help engage, recruit, and retain underrepresented participants in ADRD research.

Discussions with leadership at various Consortium sites continue to generate ways to strengthen and advance new outreach strategies through partnerships with larger online research projects with substantive Latino enrollment (e.g., MindCrowd), online and on-the-ground research projects (e.g., All of Us), and community engagement programs involving community health workers and *promotores*. However, there is a need to complement these efforts and approaches with additional professional marketing methods to extend the AAC's engagement of the Latino community and to recruit and retain a larger, more diverse pool of underrepresented participants.. Funds were used in a way that complement but do not overlap with funding provided by the NIA and other funding sources for the ancillary programs.

Year End Progress Summary:

Our AAC outreach, recruitment and retention efforts are a combination of in-person events, traditional media, and social media strategies. Many of our traditional activities were adapted as a result of the COVID-19 pandemic to include video conferencing (i.e., Zoom), Facebook and Facebook Live events, texting, and the like to reach across Arizona and serve our communities. Through an array of community outreach, recruitment, and engagement activities, over 68,000 contacts were made with our fellow Arizonans regarding AD, normal aging, and the AAC, including individuals from Arizona's populations at higher risk for ADRD. This is likely understated as it is difficult to estimate the number of listeners reached through radio and TV programs (estimated at over 100,000). The Alzheimer's Prevention Registry with over 389,600 members is led by BAI and has 50,000+ followers on its Facebook page and routinely promotes AAC studies and events. BAI's Dementia Untangled podcast which reaches people living with dementia, family caregivers, other community members, and professionals, surpassed 200,000 total plays. The podcast has reached thousands of people living with dementia, family caregivers, professionals, and the general public. Social media has also been used to help promote AAC conferences and institutional member events such as its Fall 2025 Annual AAC Statewide Scientific Meeting (over 550 attendees in person) hosted by TGEN and held at ASU, the Spring 2026 Public Conference (almost 300 people living with cognitive decline, family caregivers, providers and other interested members of the public) hosted by AAC at the ASU Health Futures Center, and other events. These conferences and related meetings provided ample outreach, recruitment and education opportunities and were organized by Dr. Coon and his team.

While we provided outreach, recruitment, education, and other services to reach people representative of Arizona's overall population, we also continue to develop, adapt, and disseminate ORE Core events and products to help reach Arizona's populations that are at higher risk for ADRD including our Native American and Latino/Hispanic populations. For example, the 19th Annual Alzheimer's and Dementia in Native Americans Conference and its complementary pre-conference was held in Flagstaff on October 29 and 30, 2025 with great success. BAI reach over 1600 community members and professionals through its Native American Dementia Friends Tribal sessions and other outreach activities. Examples of outreach and education products developed and disseminated to Arizona's Native American population include BAI's acclaimed Native American *Navigating through Memory Loss Guide* and *Native American Toolkit for human services providers/family Caregivers*, which includes *Hearing our Voices*, a video featuring Arizona tribal family caregivers sharing their personal perspectives on caring for loved ones with dementia.

Outreach into the Hispanic/Latino community encompassed English, Spanish, and bilingual activities to help reach the 20% of Arizona households where Spanish is the primary language in the home, and to help address the needs of bilingual people living with cognitive decline who tend to lose their second language fluency as ADRD progresses. Many AAC on-the-ground and online efforts progressed through local community health worker/*promotores* programs in coordination with Dr. Coon's team. Outreach and educational presentations reached over 4,000 Latino participants focused on cognitive aging, dementia, and family caregiving issues with attention paid to AAC partner offerings and research opportunities. Community education presentations have been offered in partnership with a variety of community-based. These activities were combined with individualized Zoom-based and in-person presentations to organizations such as *Valle del Sol*, Unlimited Potential, Chicanos por La Causa, *Salud en Balance*, Muhammad Ali Parkinson's Center*,* United Health Care, Equality Health, and local church and senior centers. BNI convenes its Self-care groups in Spanish and *Cafecito Network* monthly education groups and ASU makes its original CarePRO and EPIC programs available to both English and Spanish speakers. While strong connections are already in place with many community partners such as the Alzheimer's Association and local area agencies on aging, and healthcare organizations, we continue to expand our partnerships with a variety of new partnerships with organizations and entities such as All Thrive 365 (formerly, the Foundation for Senior Living), Valley of the Sun United Way, Ventanilla de Salud, Keogh Health Connections and ASU's Center for Innovation in Healthy & Resilient Aging and its NIA Roybal Center for Older Adults Living Alone with Cognitive Decline.

Social media outreach efforts this year included Facebook Live Events on multiple bilingual health/culture pages, bilingual newspapers/magazines, radio shows for the Latino community. Outreach on social media also heavily relies on cross-promotion from our community partners; and, there have been ongoing discussions with MindCrowd and All of Us about ways to target Latino/Hispanic and Native American participants to encourage enrollment in Arizona Alzheimer's Consortium activities. We continued to work with a local professional marketing firm with established experience in the Latino community to advance our AAC campaign and engage, recruit, and retain Latino participants in ADRD research. The firm has continued to develop social media assets for our AAC Public Conference helping to increase awareness and attendance. With regard to other assets, we share via our website and social media platforms, *Latino Personal Stories* video clips developed by ASU and BNI that feature Arizona Hispanic/Latino families sharing their thoughts about caring for family members with ADRD.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Quantifying Micro- and Nanoplastics in the Aging Brain: Associations with Alzheimer's Disease Pathology and Socioeconomic Disadvantage. Diego Mastroeni, PhD, Amy Kind, MD, PhD, Thomas Beach, MD, PhD, Geidy Serrano, PhD, Ben Readhead, MBBS, Charles Rolsky, PhD, James Brown, PhD, Zoe Arvanitakis, MD, Jeremy Pruzin, MD. Arizona State University; University of Wisconsin-Madison; Banner Sun Health Research Institute; Shaw Institute; Rush University Medical Center; Banner Alzheimer's Institute, Arizona Alzheimer's Consortium.

Specific Aims:

1. Quantify the presence and level of micro- and nanoplastics (MNPs) in the prefrontal cortex (PFC) and Cerebral Spinal Fluid (CSF) using four advanced analytical techniques in brain donors.
2. Examine associations between MNP levels and Alzheimer's disease (AD) pathology, adjusting where feasible for age, sex, and APOE genotype.

Background and Significance:

Micro- and nanoplastics (MNPs) are ubiquitous environmental pollutants with emerging evidence of accumulation in human tissues, including brain. Because MNPs may cross the blood-brain barrier, induce neuroinflammatory responses, and exacerbate AD-like pathology in experimental models, there is a critical need to determine whether polymer-specific MNP burden can be detected in well-characterized human brain tissue and whether burden differs by neuropathological diagnosis. This project leverages the Banner Sun Health Research Institute Brain and Body Donation Program and collaborators with expertise in neighborhood-level environmental risk to generate pilot data linking analytical MNP measures with neuropathological and clinical covariates in aging and dementia.

Preliminary Data, Experimental Design and Methods:

The approved project proposed analysis of 25 brain donors with matched brain tissue and CSF (50 samples total). During the reporting period, we prioritized Pyrolysis-Gas Chromatography/Mass Spectrometry (Py-GC/MS) as the first quantitative polymer-analysis platform because it provides polymer identity and concentration in complex tissue matrices.

Matched sample identifiers were cross-referenced to BBDP case information, including diagnosis group, age, sex, postmortem interval, APOE genotype, MMSE, Braak stage, plaque burden, tangle burden, Lewy body measures, and neuropathological diagnosis. The final corrected cohort included 15 AD cases, 5 Parkinson's disease (PD) cases, and 5 controls, with matched brain and CSF for each donor.
Quality-control emphasis included correction and verification of sample mapping, polymer-specific quantification, and conservative interpretation of results given the small pilot sample size and the destructive nature of Py-GC/MS. Orthogonal methods, including Raman/FTIR-based approaches and Nile Red/flow-based workflows, remain important for validation and particle-level characterization, particularly because Py-GC/MS quantifies polymer mass and identity but does not provide particle size, number, or spatial distribution.

Proposed One-Year and Long-Term Outcomes:

One-Year Outcomes: Complete quantification of MNPs in all 25 brain/CSF donors; finalize and validate a multi-method detection protocol; conduct statistical analysis of MNP-AD associations and preliminary ADI findings; and submit at least one manuscript and conference abstract.

Long-Term Outcomes: Establish cerebral MNPs as a potential environmental risk factor for neurodegeneration; inform multi-cohort studies examining pollution and brain health; provide foundational data for mechanistic studies of MNP-induced neuroinflammation; and contribute to public health policy development targeting pollution-related brain aging.

Year End Progress Summary:

Substantial progress was made toward the proposed one-year outcomes. First, the project successfully moved from feasibility work into direct human brain and CSF measurement. We completed Py-GC/MS quantification for the planned 25 matched donors, generating polymer-specific data from both cortical brain tissue and CSF. The final corrected sample map included 15 AD cases, 5 PD cases, and 5 controls. All sample IDs were matched to BBDP clinical and neuropathological metadata, enabling integrated analysis of MNP burden with diagnosis group, Braak stage, plaque burden, tangle burden, Lewy body measures, APOE genotype, age, PMI, and cognitive measures.

Second, the Py-GC/MS analyses demonstrated detectable polymer burden in human brain tissue across diagnosis groups, with polyethylene (PE) contributing the dominant signal in most samples. In the corrected analysis, total brain/OSG plastic burden differed across diagnosis groups (Kruskal-Wallis $p = 0.042$). AD cases had higher brain/OSG total burden than controls (AD mean = 18.92 μg/mg, median = 9.27 μg/mg; controls mean = 5.41 μg/mg, median = 3.98 μg/mg; Mann-Whitney $p = 0.0146$). PD cases also showed numerically higher burden than controls (PD mean = 14.50 μg/mg, median = 8.72 μg/mg), although this comparison did not reach conventional statistical significance in the small pilot sample ($p = 0.056$). AD and PD did not differ significantly from each other ($p = 0.93$).

Third, the matched CSF analyses produced a different pattern. CSF total plastic burden did not differ significantly across Control, PD, and AD groups (Kruskal-Wallis $p = 0.355$), and the correlation between CSF and brain/OSG total burden was weak (Spearman rho = 0.21, $p = 0.32$). These results suggest that, at least in this pilot dataset, CSF polymer burden may not directly mirror total cortical polymer mass. This is an important negative/neutral result that will guide future sampling and biomarker-development strategies.

Fourth, we performed exploratory association analyses within disease-relevant strata. Across all cases, brain/OSG total burden was associated with age (Spearman rho = 0.42, $p = 0.035$), but total burden did not show strong correlations with Braak stage, plaque total, or tangle total across the mixed cohort. More importantly, within the AD group, total brain burden did not clearly scale with Braak stage, plaque burden, or tangle burden, suggesting that the observed AD/control difference may reflect disease-group, exposure-history, tissue-vulnerability, clearance, or cohort-level factors rather than a simple linear relationship with end-stage plaque/tangle severity. Within PD cases, brain burden did not clearly track with Lewy body density; possible trends with PD duration and age were observed but were limited by $n = 5$.

Within controls, there was no clear association between brain burden and age.

Fifth, APOE analyses were conducted as exploratory covariate analyses. In AD cases, APOE4 noncarriers had higher brain/OSG total burden than APOE4 carriers (noncarrier mean = 28.03

μg/mg, median = 22.69 μg/mg; carrier mean = 8.51 μg/mg, median = 7.35 μg/mg; Mann-Whitney p = 0.014). However, this finding was attenuated after considering age and is being interpreted cautiously as hypothesis-generating rather than definitive. PD cases could not be meaningfully evaluated for APOE effects because all 5 PD cases were APOE 3/3, and the control group included only one APOE4 carrier.

Several challenges were encountered and addressed. The most important was identification of a corrected sample order after initial analysis suggested that several samples had been mixed in the original file. We therefore rebuilt the crosswalk from the corrected ASU sample file rather than relabeling the prior workbook and reran all group comparisons and correlations. This correction materially changed the interpretation and produced a more coherent AD/control brain-burden signal. Additional limitations include small group sizes, limited power for stratified analyses, the destructive nature of Py-GC/MS, and the inability of Py-GC/MS alone to determine particle size, particle number, or tissue spatial distribution. ADI analyses were not completed in this first reporting period and remain dependent on final linkage of life-course residential/ADI data to the analyzed donors.

Overall, the project met the primary technical objective of generating quantitative polymer-specific Py-GC/MS data from the planned matched brain/CSF donor set and made strong progress toward the biological objective of assessing relationships with AD-related neuropathology. The data support a focused manuscript describing polymer-specific plastic burden in matched human brain and CSF across AD, PD, and controls. The findings also provide preliminary data for larger external grant applications that will expand the cohort, incorporate orthogonal particle-level validation methods, and test whether MNP burden relates to environmental exposures, neighborhood disadvantage, neuroinflammation, and disease-relevant molecular pathways.

Products, Collaborations, and Next Steps:

This AAC-supported work strengthened collaborations among Arizona State University, Banner Sun Health Research Institute, Banner Alzheimer's Institute, Shaw Institute, Rush University Medical Center, and the University of Wisconsin-Madison. **Importantly, preliminary data generated through this AAC-supported project were incorporated into a recently funded NIH R21 application (R21ES038336-01A1), providing immediate external leverage for this pilot work**. A manuscript and conference abstract are in preparation. Next steps include final analytical chemistry QC review, orthogonal validation of selected high- and low-burden cases, ADI linkage, and preparation of a larger multi-cohort grant application.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Surgical Menopause-Induced Alterations in Cellular and Activity-Dependent Processes in the Rodent Forebrain. Jason Newbern, PhD, Heather Bimonte-Nelson, PhD, Juliana Kling, MD, MPH. Arizona State University; Arizona Alzheimer's Consortium; Mayo Clinic Alix School of Medicine.

Specific Aims:

Specific Aim 1. To determine whether there are selective vs widespread changes in the patterns of activity dependent protein expression within core forebrain regions following behavioral stimulation in cognitively demanding tasks.

Specific Aim 2. To assess whether alterations in chronic activity dependent protein expression in cognitively relevant forebrain circuits coincide with altered glial activation within the grey matter and patterns of myelination and oligodendrocyte turnover within the associated white matter.

Background and Significance:

This proposal centers on understanding the neurological effects of reproductive surgery in aging women, particularly hysterectomy and oophorectomy, which are common and often occur before natural menopause. These surgeries have been associated with increased risks of cognitive deficits, including anxiety and dementia, yet the mechanisms linking uterine-ovarian function to CNS health remain poorly understood. Potential pathways include changes in canonical hormones such as estrogen, progesterone, LH, and FSH; loss of uterine- and ovarian-derived signaling factors such as Wnts, LIF, and EGF; systemic effects on metabolic, cardiovascular, and immune systems; and peripheral or vagal connectivity between reproductive organs and the nervous system. The project aims to identify the forebrain circuits and cellular subtypes that may mediate cognitive changes following surgical menopause. Using brain tissue from rats that underwent hysterectomy or oophorectomy and completed extensive cognitive testing, the study will examine cellular composition and activity-dependent protein expression within cholinergic-prefrontal circuits. Preliminary findings suggest selective neural circuit imbalances associated with loss of ovarian and uterine-derived cues. By leveraging these valuable samples, the project seeks to define mechanisms underlying surgery-associated cognitive changes and support future biomarker development, precision medicine approaches, and targeted therapeutic strategies for women's brain health during aging.

Preliminary Data, Experimental Design and Methods:

Preliminary studies used rats assigned to Sham, hysterectomy, or ovariectomy groups, followed by a battery of demanding spatial learning and memory tasks. Brain tissue was collected within two hours of behavioral testing to preserve activity-dependent molecular signatures. Initial multiplex immunolabeling and high-resolution confocal imaging focused on the basal forebrain and medial prefrontal cortex, using markers for neurons, VIP-expressing GABAergic cells, activity-dependent CFOS expression, and nuclei. Early analyses suggest that removal of the uterus or ovaries does not produce broad loss of core neuronal subtypes in the regions examined, despite associated cognitive changes. Instead, the preliminary data pointed toward altered activity-dependent protein expression within specific neuronal populations.

The proposed work will test this idea across forebrain regions important for memory, anxiety, and executive function, such as the medial prefrontal cortex, hippocampus, and basal forebrain. Specific Aim 1 will use multiplex immunolabeling for neuronal subtype markers and activity-dependent proteins such as FOS, FOSB, and ARC to identify which neuronal populations show abnormal activation after hysterectomy or ovariectomy. Specific Aim 2 will examine whether cognitive effects are also associated with glial changes, immune-related activation, or altered

myelination in key gray and white matter regions. This will include analyses of astrocytes, microglia, oligodendrocytes, and myelin markers, as well as a pilot mouse study to assess tools for examining myelination of basal forebrain cholinergic fibers. Together, these studies aim to define the cellular and circuit-level mechanisms linking reproductive surgery to cognitive change.

Proposed One-Year and Long-Term Outcomes:

At the completion of the one-year project period, we will have completed the planned immunostaining experiments, high-resolution confocal imaging, and digital imaging analysis of the rat brains described above. Following data analysis of cellular density and/or patterns of activity dependent protein expression and myelination, we will compile our results into a manuscript to be submitted within 6 months of completing this work. Parallel efforts with Dr Bimonte-Nelson's laboratory will correlate our cellular and circuit level data with behavioral and cognitive data previously collected. Indeed, we fully plan to utilize these findings as preliminary data in an NIH R01 level submission to the NIH or other foundation sources, one of which has already been submitted based on the data collected during the last funding cycle. This planned grant submission will be focused on understanding how surgical menopause variants modulate brain circuitry in a larger range of areas relevant to cognition. This work will inform efforts to develop biomarkers and rationally design precision therapeutic approaches meant to maximize women's health during aging and menopause.

Year End Progress Summary:

During the current project period, we made substantial progress toward defining how surgical menopause variants alter cellular and activity-dependent processes within cognition-relevant forebrain circuits. We successfully collected brain samples from rats that underwent Sham surgery, hysterectomy, or ovariectomy, followed by extensive behavioral testing in high-demand learning and memory tasks. Because these rats were collected within two hours of behavioral testing, the tissue provides a unique opportunity to evaluate cellular and molecular signatures in a behaviorally stimulated state. All brain samples required for the proposed analyses had already been perfusion fixed, cryopreserved, and stored in Dr. Newbern's laboratory. During this reporting period, we conducted brain sectioning, immunostaining, confocal imaging, and digital image analysis of multiple samples, with an emphasis on forebrain circuits implicated in memory, anxiety, and executive function.

A major focus of this work was to expand and optimize multiplex immunolabeling strategies for detecting core neuronal subtypes and activity-dependent protein expression in the medial prefrontal cortex, hippocampal formation, basal forebrain, and related circuitry. We conducted high-resolution confocal microscopy using established neuronal markers, including NeuN/RBFOX3, markers of inhibitory neuronal subtypes, and activity-dependent proteins. These experiments demonstrated that the available tissue is well suited for high-content analysis of cell density, subtype identity, and activity-dependent protein expression. Preliminary analyses from selected regions suggest that hysterectomy and ovariectomy do not produce broad loss of core neuronal populations in the regions examined to date. Instead, the emerging pattern points toward selective changes in activity-dependent protein expression within specific neuronal subtypes. These findings support our working hypothesis that cognitive alterations following loss of ovarian-or uterine-derived cues may reflect abnormal recruitment of specific neural circuits rather than overt degeneration or loss of major neuronal populations, but additional quantification will be necessary.

Progress was also made toward Specific Aim 2, which focuses on glial activation, immune-related changes, and myelination within gray matter and associated white matter tracts. We initiated staining and analysis strategies for astrocytes, microglia, and myelin-associated markers, including GFAP, Iba1, and MBP designed to determine whether altered cognitive performance

following hysterectomy or ovariectomy coincides with changes in glial state, white matter organization, or oligodendrocyte-related processes in forebrain pathways. Some antibody optimization has been required, particularly as we refine staining conditions across multiple brain regions and tissue batches. However, the core staining approaches are now working as expected, and image acquisition and blinded analysis are ongoing. We are also continuing to refine image-analysis workflows using confocal microscopy and digital quantification pipelines to measure cell density, marker co-expression, and fluorescence intensity in anatomically defined regions.

Due to the extensive multiplex histology across multiple brain regions and surgical conditions, the pace of data generation is shaped significantly by the time-intensive nature of cryosectioning, immunostaining, high-resolution confocal microscopy, and blinded image analysis. Minor delays were observed during the funding period due to technical issues with select antibody staining protocols and the confocal detector that were resolved and the project has advanced substantially. We have established the foundation for the proposed analyses, confirmed the quality and utility of the tissue, generated preliminary evidence for selective circuit-level alterations, and begun extending the work into glial and myelination endpoints. These data are helping to clarify which cell types and forebrain regions are most sensitive to loss of uterine- and ovarian-derived cues, and they provide a framework for linking cellular phenotypes with the cognitive and behavioral outcomes already collected in collaboration with Dr. Heather Bimonte-Nelson's laboratory.

These efforts have also supported important long-term outcomes. The project continues to strengthen an interdisciplinary collaboration among Dr. Newbern's laboratory, Dr. Bimonte-Nelson's behavioral neuroscience program, and clinical collaborators focused on women's health and menopause-related cognitive change. Preliminary data and the conceptual framework from this work have contributed to ongoing and pending grant applications focused on menopause, cognition, and brain aging, including NIH- and foundation-level funding efforts. The data being generated from this project are expected to support at least two manuscripts focused on surgical menopause-associated changes in forebrain cellular and activity-dependent processes. More broadly, this work is providing mechanistic insight into how hysterectomy and ovariectomy may alter cognition-relevant neural circuits, with the long-term goal of identifying biomarkers and therapeutic targets that could improve brain health outcomes for women during aging and menopause.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Standardization of Conductivity Tensor Imaging Protocols for Characterizing Alzheimer's Disease. Rosalind Sadleir, PhD, Yuxiang Zhou, PhD, Bryan Woodruff, MD. Arizona State University; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

Development of imaging biomarkers for Alzheimer's Disease (AD) and AD related dementias (ADRD) are important for understanding changes in brain structure and function; identifying those with risk of developing them, and measuring responses to treatments. In this studies we propose using magnetic resonance electrical conductivity imaging to produce **quantitative** maps that combine **tissue structure**, **diffusivity** and **composition, enabling the early identification of subtle brain alterations**. We anticipate this will enable sensitive detection of changes that may occur as structural and cognitive damage starts. Conductivity tensor imaging (CTI) reconstructs low-frequency (<100 Hz) conductivity images that reflect membrane permeability, cell density, and morphology. CTI **combines** high-frequency conductivity images (EPT) measured at 128 MHz — sensitive to ionic composition, with multi-shell diffusion data — sensitive to tissue microstructure, allowing detailed assessment of both factors. We have predicted low-frequency conductivities (CTI) using microstructure parameters extracted from DWI databases of AD and mildly cognitive impaired (MCI) patients, APOE-□4 positive subjects and age-matched controls. Our preliminary data, as well as data from another recent study, suggest that CTI metrics have the potential to detect conductivity differences between AD or MCI patients and controls. However, prior to implementing this quantitative technique, it is extremely important to validate our methods across imaging platforms and to produce the maximum possible conductivity sensitivity and precision.

These studies have the eventual goal of establishing CTI as a sensitive clinical tool for detecting early brain abnormalities and differentiating AD from ADRD. The proposal has two aims: to harmonize CTI measurements across platforms and verify their precision, and to collect pilot imaging data to establish a database in cognitively normal individuals and assess sensitivity in those with mild cognitive impairment (MCI).

AIM 1: ***Refine CTI imaging protocols.***

In **Aim 1** we will adapt our existing B1 mapping and DWI protocols for measurement of brain tissue electrical properties precisely. We have already established a protocol designed for testing CTI on a Siemens platform. We will adapt our protocol to GE scanners, which have more restrictive parameter sets. Outcomes of Aim 1 are CTI imaging protocols on Siemens and GE platforms with common relative resolution and signal to noise (SNR) > 200 in vivo.

In **Aim 2** we will perform a pilot study of MCI subjects against age-matched controls with the CTI protocol on each scanner type to determine if CTI conductivity changes predicted by preliminary data are maintained in humans. Outcomes of Aim 2 are indications of CTI's sensitivity and specificity to MCI within the hippocampus, and an overview of other structures that may be differentially affected by AD. We anticipate that results will form the basis for differential diagnosis of AD against related dementias including Lewy Body Dementia.

Background and Significance:

Alzheimer's Disease (AD) is a ubiquitous and disruptive feature of aging populations, with an estimated 6.7 million Americans age 65 and older experiencing Alzheimer's dementia[1]. Low-frequency electrical conductivity measures are potentially a key indicator of pathological changes

in the brain at different stages of Alzheimer's disease, because conductivity depends upon both tissue composition and ionic mobility.

Preliminary Data, Experimental Design and Methods:

The high frequency EPT contribution to CTI alone varies significantly in MCI patients. Previous studies indicated that electrical conductivity of gray matter in AD patients was increased by around 30% at 200 MHz compared to age matched controls. We expect a similar or even larger distinction at 3T (corresponding to 128 MHz), as tissue differences are typically more prominent at lower frequencies. A second pilot clinical study using CTI, indicates that high frequency conductivity in hippocampus was significantly higher in MCI compared with age-matched cognitively normal subjects, although addition of their diffusion microstructure analysis did not yield significant results.

Added value from diffusivity information Low-frequency conductivity properties relate to intra-and extracellular diffusivity. These properties relate closely to tissue microstructure and can be estimated using diffusion microstructure modeling. Microstructure modeling enables detailed assay of tissue structure cellular density and organization. Evidence from collaborators showed that a microstructure index derived from Neurite Orientation Dispersion and Density Imaging (NODDI) analysis of diffusion microstructure data, neurite density index, was significantly decreased in APOE-□4 subjects. We also published evidence that NODDI and other diffusion microstructural analysis methods that model both white and grey matter may provide better sensitivity to brain structural and compositional changes. Therefore, we anticipated higher sensitivities in vivo when real EPT data are obtained but need to ensure EPT data have high SNR to ensure changes are distinct.

Proposed One-Year and Long-Term Outcomes:

These studies will provide invaluable preliminary data establishing the ability of CTI to assess brain conductivity and an initial indication of its power to distinguish characteristics present in MCI patients compared to cognitively normal controls. We intend using these data in further assessments of both EPT and diffusion microstructure protocols and models to distinguish characteristics of Alzheimer's disease from other dementias and neurodegenerative diseases, and determining predictive powers of CTI measures combined with cognitive and other measures.

Year End Progress Summary:

We have achieved Aim I, wherein we harmonized Siemens and Philips sequences for imaging high-frequency electrical conductivity maps. Data on either platform were confirmed to have SNR values > 250 when image parameters were matched as closely as possible. Imaging times were restricted to around 8 minutes for sequences.

We performed image harmonization by testing each sequence using an imaging phantom consisting of three vessels containing fluids with distinct electrical conductivities. The same phantom was used to image high-frequency conductivity on each platform. We encountered some issues in completely reconstructing data using GE platforms, but Dr. Zhou worked closely with GE personnel to complete this task under the Mayo Clinic-GE research agreement.

We are currently preparing a paper comparing high-frequency electrical conductivity measured using each platform and the test phantom.

Aim 2 of the study was altered in response to reviewer comments received in review of an R01 proposal submitted during the project period, details of these changes are given below.

In a previous study, pilot data was collected using the GE implementation of the combined conductivity tensor imaging protocol consisting of both multi-b value diffusion and high-frequency conductivity studies. Subjects in this study were older, cognitively normal adults. This will be combined with data we have collected over the project duration using Knowledge Donor (KD) subjects. We elected to use decedent KD subjects because we recognized the need to characterize data from subjects at as high a SNR as possible (i.e. without movement artefact) and in older adults to directly compare against our earlier in vivo data. In order to harmonize these data against each other we have also included scans in our studies that characterize KD subject MRI relaxation times. A paper on this topic authored by the Masters' student employed on this project was submitted to the International Society for Magnetic Resonance in Medicine annual meeting held in Johannesburg, South Africa (9-14 May) and presented as a digital poster. We found that relaxation times and therefore our electrical conductivity and diffusion measures are broadly similar to those found in vivo, unlike tissues preserved with formalin.

At present, we are completing our parallel analysis of KD and in vivo data from older adults to form a solid database of normal CTI data. These analyses, in combination with further analysis of recent ADNI data comparing diffusion in subjects with mild cognitive impairment and age-matched controls will be used as the basis of our R01 proposal resubmission, anticipated to be in October 2026. Three manuscripts are in preparation arising from this work.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Unraveling the aged tau species that develop as a consequence of normal aging. Jui-Heng Tseng, PhD. Arizona State University; Arizona Alzheimer's Consortium.

Specific Aims:

Tau pathology is closely linked to neurodegeneration in aging and Alzheimer's disease (AD), yet how tau changes during normal aging remains poorly understood. We recently identified a distinct form of tau that accumulates in aged wild-type mice, characterized by altered localization and acetylation without classical phosphorylation. We term this species "aged tau" and hypothesize that it represents an early, pre-pathological tau species that emerges during normal brain aging.

Aim 1: Characterize tau evolution during normal brain aging: We will identify age-associated tau post-translational modifications (PTMs) in cognitively normal human brains and determine whether HDAC3 and HDAC6 regulate tau acetylation across aging.

Aim 2: Dissect the molecular mechanisms by which aged tau alters neuronal function: We will investigate how aged tau impacts microtubule structure and mitochondrial dynamics to define early cellular changes that precede neurodegeneration.

This work will define the molecular signature of aged tau and establish its role in early neuronal dysfunction, providing insight into mechanisms that link normal aging to AD.

Background and Significance:

Tau pathology is a defining feature of Alzheimer's disease, yet the earliest molecular events that initiate tau dysfunction remain unclear. While current diagnostics detect late-stage, aggregated tau, these changes are likely irreversible, highlighting the need to identify earlier alterations.

This project investigates how tau PTMs, particularly acetylation and phosphorylation, arise during normal aging and contribute to the initial steps of pathology. Preliminary data show that acetylated tau accumulates in the hippocampus of aged wild-type mice, but not in young mice, suggesting it represents an early, pre-pathological tau species.

This study will characterize age-dependent tau PTMs, determine the role of HDACs in regulating these modifications, and define how these changes impact neuronal function using biochemical and structural approaches. By identifying the earliest tau alterations during aging, this work aims to enable the development of early biomarkers and inform strategies to intervene before irreversible neurodegeneration occurs.

Preliminary Data, Experimental Design and Methods:

Aim 1: Characterizing tau evolution during normal brain aging: We have begun defining age-associated tau PTMs, focusing on an early "aged tau" species enriched in acetylation. To improve rigor and control, we transitioned to a rodent aging model and established a C57BL/6 cohort spanning 3 to 12 months. We are generating tau PTM profiles using mass spectrometry, immunohistochemistry, and biochemical approaches. In parallel, we are evaluating HDAC3 and HDAC6 as regulators of tau acetylation by assessing their expression, activity, localization, and interaction with tau. These studies are beginning to reveal age-dependent shifts in tau modification and potential regulatory mechanisms.

Aim 2: Determining how aged tau disrupts neuronal function: We have initiated studies to define how tau species impact microtubule integrity and mitochondrial function. We observe tau-dependent changes in tubulin post-translational modifications, consistent with altered microtubule stability. In parallel, we established workflows to assess mitochondrial dynamics, morphology, and bioenergetics, including ATP measurements and Seahorse assays.
Preliminary results indicate that distinct tau species are associated with altered mitochondrial structure and function.
Overall, these approaches are enabling us to define the molecular features, regulation, and functional impact of aged tau during normal aging.

Proposed One-Year and Long-Term Outcomes:

0 – 12 months: Acquire human brain tissue from brain repositories and analyze tau PTM evolution by mass spectrometry, immunohistochemistry, and biochemistry in human brains during normal aging. Analyze and probe HDAC3 and HDAC6 in human brain tissue as a function of aging.
12 – 24 months: Complete mass spectrometry analysis to identify age-associated tau PTM signatures in human brain tissue. Generate tau constructs representing key aging-associated tau signatures and determine their effects on neuronal and mitochondrial function. Validate findings, prepare manuscripts, and submit an NIH/NIA R01 application.
Long-term outcomes: This project will define age-associated tau signatures and establish their functional impact on neuronal and mitochondrial homeostasis. These findings will provide insight into the earliest molecular changes in brain aging, identify potential biomarkers and therapeutic targets, and support future NIH/NIA R01 funding.

Year End Progress Summary:

- **Progress made towards the proposed one-year outcomes.**

Aim-1. We shifted our approach from studying human aging to using a rodent aging model due to concerns about the quality of non-demented young human brain tissue, particularly the longer postmortem intervals that may compromise molecular analyses. Restricting our studies to only high quality human samples would substantially limit sample size and reduce statistical power, making it difficult to obtain robust and reliable results. Instead, we initiated tissue collection from C57BL/6 wild-type mice across the aging spectrum. To date, we have collected 3 mice at 3 months of age (all male), 9 mice at 9 months of age (3 female, 6 male) and 8 mice at 12 months of age (6 female, 2 male). Based on our current collection schedule, we anticipate completing the planned cohort of 10 mice per age group (50% male and 50% female) across four time points (3, 6, 9, and 12 months) by the end of June. We plan to prepare these samples for mass spectrometry analysis at our collaborator Dr. Tsui-Fen Chou's mass spectrometry facility at Caltech by the end of the summer.
Aim 2. We completed a series of experiments to examine how distinct tau species alter microtubule organization and mitochondrial function. We assessed the impact of acetylated tau and pathological tau variants on microtubule stability by measuring tubulin post translational modifications, including acetylation, detyrosination, and polyglutamylation. To evaluate mitochondrial effects, we performed studies in HEK cells and primary mouse neurons to define the physiological role of tau in mitochondrial function and how this is altered during aging and disease. Mitochondrial dynamics were assessed by analyzing key fission and fusion proteins. In addition, we established a quantitative workflow to analyze mitochondrial network morphology using confocal microscopy and downstream image analysis. For functional assessment, we

measured ATP levels in HEK cells and primary neurons expressing different tau species. We also established a collaboration with Dr. Shu Wang at Arizona State University to implement Seahorse assays for measuring oxidative phosphorylation.

- ***Findings and explanation for any challenges encountered.***
  For Aim 1, the transition to a rodent aging model has enabled the generation of a well-controlled and high-quality tissue cohort spanning defined stages of aging. This approach overcomes key limitations associated with human brain tissue, including variability and extended postmortem intervals, and positions us to produce statistically powered and mechanistically informative datasets. Cohort establishment and tissue collection pipelines are now fully operational, and sample acquisition is proceeding on schedule toward completion. These samples are expected to yield high-resolution mass spectrometry datasets defining age-dependent molecular signatures relevant to neurodegeneration.
  For Aim 2, our findings provide strong evidence that distinct tau species actively regulate both microtubule integrity and mitochondrial function. We identified tau-dependent remodeling of tubulin post translational modifications, consistent with direct effects on microtubule stability. In parallel, we observed robust alterations in mitochondrial dynamics and bioenergetics, including changes in fission and fusion protein profiles, mitochondrial network architecture, and cellular ATP levels. Together, these data support a model in which disease-associated tau disrupts cytoskeletal organization and mitochondrial homeostasis. We have established and validated integrated experimental platforms combining quantitative imaging, biochemical assays, and Seahorse-based metabolic profiling through collaboration with Dr. Shu Wang, enabling comprehensive and scalable analysis of mitochondrial function.

  Initial challenges included variability in primary neuron cultures and optimization of mitochondrial imaging and analysis workflows. These issues have been effectively resolved through protocol standardization and iterative refinement, resulting in reproducible and high-quality datasets. The experimental systems developed here are now fully established and are directly supporting ongoing mechanistic studies and manuscript preparation.

- ***Describe progress made on the proposed long-term outcomes. Include future grant applications, publications and collaborations that arose from the research.***
  Over the past year, we have actively pursued external funding to support our studies on tau PTMs and their roles in normal aging and disease. This work has resulted in submissions to the Alzheimer's Association Research Grant, NIH/NINDS R01, NIH/NIA R21, the 2026 Rainwater Tauopathy Workshop application, the Arizona Biomedical Research Centre New Investigator Award, and the Edson Initiative New Idea Fund. We have just submitted an NIH/NIA R01 application for the June 2026 cycle.
  On the publication front, we published an invited review article on tau post-translational modifications in normal aging and neurodegenerative disease in Frontiers in Dementia, and submitted a manuscript currently being reviewed in iScience.

  In addition, we have continued to establish collaborative research relationships within and beyond ASU, including with Drs. Bert Jacobs and Ian Hogue in ASU SOLS, Dr. Shu Wang from ASU CHS, Dr. Tsui-Fen Chou from Caltech, and Dr. Xu Hou from Mayo Clinic Jacksonville.
  These collaborators are serving as mPI or co-investigators on the grant applications described above.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Cerebellar pathology in Alzheimer's disease from a translational model to humans. Jessica Verpeut, PhD, Sylvia Perez, PhD, Elliott Mufson, PhD. Arizona State University; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Specific Aims:

Specific aim 1: Analyze genetic contributions to cerebellar structure and perineuronal nets to compare with cognitive test scores in human Alzheimer's disease brain samples.

Specific aim 2: Examine perineuronal nets and the tetrapartite synapse in the cerebellum of TgF344-AD rats in relation to changes in cognitive and fine motor behavior.

Background and Significance:

The role of the cerebellum in cognitive aging is largely unexplored compared to the hippocampus and prefrontal cortex, but emerging evidence suggests that the cerebellum undergoes structural and functional changes during aging. These changes include decline in synaptic plasticity, increased neuroinflammation, and decreased cerebellar-cerebral connectivity. There is neurobiological feasibility for the view that the cerebellum systematically contributes to behavior and changes in the brain associated with Alzheimer's disease (AD), including bidirectional pathways from the cerebellum to brain regions associated with memory formation, episodic/spatial memories, and cognition. Moreover, interruptions to this circuitry, documented in adult clinical cases with cerebellar injuries, are typically marked by disruptions to executive function, working memory, language, and emotional disturbances.

The cerebellar cortex has been hypothesized to show minimal AD-associated pathologies with aging and may have neuroprotective properties that explain less age-related pathology. Unlike the cerebellar cortex, discrete cerebellar nuclei (CN) display abundant neurodegenerative pathology including tau accumulation, cell atrophy, Lewy body accumulation, and changes in cell cycle expression in AD. Others have proposed that weaker astrocyte-microglia interactions and increased reactive glia, lead to a breakdown of plasticity through the extracellular matrix, including perineuronal nets and atrophy of neural dendrites and axons in AD. Relationships between glia and the extracellular matrix on neural plasticity are known as the tetrapartite synapse. While this has been studied in detail in the hippocampus, the cerebellum is understudied. To study these mechanisms, we will examine human cerebellar tissue samples to understand changes in genes and perineuronal nets in AD then use a preclinical rat, the TgF344-AD model, to probe the biological mechanisms that underlie changes in cerebellar neural structure that may influence behavior.

The ***objective*** of this proposal is to study changes in cerebellar genes, neural structure, and behavior in Alzheimer's disease. We ***hypothesize*** that cerebellar genes will be altered in human patients with an AD diagnosis. We further ***hypothesize*** that TgF344-AD rats will have increased glia and reduced perineuronal nets, reducing plasticity for learning and memory.

Preliminary Data, Experimental Design and Methods:

Similar to the cerebellum, the precuneus is known to display hypometabolism, functional disconnection, synaptic failures and β-amyloid pathology early in AD, but little to no tangle pathology. In collaboration with Dr. Sylvia Perez and Dr. Elliott Mufson at Barrow Neuroscience Institute (BNI), gene array sequencing was performed in the precuneus of cases with a diagnosis of AD, mild cognitive impairment (MCI), and non-cognitive impairment (NCI) from the Religious orders study (RROS). We found largest changes in perineuronal net (PNN) gene expression gCOLA1, COLA2, HAPLN3, HSPG2, PODN, and SPON1 in the precuneus in AD and MCI,

suggesting that the extracellular matrix is impacted early in AD. The most abundant PNN proteoglycan is aggrecan, which is *reduced in dementia, particularly in AD, suggesting that alterations* to PNNs may underlie AD pathogenesis. In collaboration with Dr. Perez and Dr. Mufson, we found significantly reduced aggrecan in the cerebral cortex of RROS MCI (n=9; p=0.036) and AD (n=11; p=0.0003) compared to NCI (n=12) cases. Moreover, cerebellar aggrecan counts correlated significantly with episodic memory and global cognitive scores, indicating a critical role of cerebellar matrix aggrecan in cognition status. Therefore to understand the role that PNNs play in cerebellar plasticity in AD, we will examine gene expression with a focus on the extracellular matrix using RNA sequencing (**Aim 1**). The proposed studies (**Aim 2**) will parallel these changes in animal models where we will discreetly evaluate age and dissociate normal from pathological aging.

Proposed One-Year and Long-Term Outcomes:

Aim 1 tissue collection and RNA analysis in months 0-6. Aim 2 brain tissue, already collected for 12 and 18 months of age, will be processed in months 0-3 until the final tissue collection at 24 months in Fall 2025. Quantification of all samples will be completed in months 6-10. We will complete the manuscript and the next grant in months 10-12. This grant will provide preliminary data for a R01 application to the National Institute on Aging (PA-19-056). My graduate student, Alexandria Melick, is leading this project and will present this work at the Arizona Alzheimer's consortium conference and the Society for Neuroscience in Fall 2025.

Year End Progress Summary:

One-year outcomes: Cerebellar human brain tissue samples were obtained from the Rush Religious Orders Study (RROS), in collaboration with Elliott Mufson and Sylvia Perez (Barrow Neurological Institute). Comparisons were made between non-cognitively impaired controls (NCI; n = 12; mean age 87.15 ± 6.23 years; 8 females, 4 males), individuals with mild cognitive impairment (MCI; n = 8; mean age 93.4 years; 6 females ,2 males), and individuals with clinically and neuropathologically confirmed mild to moderate Alzheimer's disease (AD; n = 11; mean age 94.27 ± 6.23 years; 9 females, 3 males).

To understand changes in the tetrapartite synapse, both PNNs (brevican and aggrecan) and glia (Iba1 and HLA-DR) were measured. Brevican intensity was significantly higher than Aggrecan in the granular layer across NCI ($p = 0.0086$), MCI ($p = 0.0047$), and AD ($p = 0.0004$). While no significant group differences were found in immunomarkers for Iba1 or HLA-DR, HLA-DR intensity exceeded Iba1 intensity in the granular layer, white matter, and molecular layer (Mann-Whitney U, $p \leq 0.0007$). This suggests that cerebellar microglia are more likely to be in their active state in aged samples.

In addition, analysis of cerebellar structure revealed loss of myelin, as measured by myelin basic protein (MBP), in AD. Intensity of MBP was reduced in AD compared to NCI ($p = 0.0015$) and MCI ($p = 0.0028$) in the granule layer, as well as cerebellar white matter in AD compared to NCI ($p = 0.0232$). Strong positive correlations were found between granule layer MBP intensity and global cognitive scores ($\rho = 0.65$, $p = 0.000049$), episodic memory ($\rho = 0.64$, $p = 0.00009$), visuospatial performance ($\rho = 0.59$, $p = 0.0004$), and MMSE ($\rho = 0.51$, $p = 0.0038$). Negative correlations were found between granule layer MBP intensity, Braak stage ($\rho = -0.65$, $p = 0.00006$), and amyloid plaque burden. Therefore, cerebellar demyelination is a strong correlate of cognitive decline in AD.

Next we analyzed PNNs and the tetrapartite synapse in the cerebellum of TgF344-AD rats in relation to changes in cognitive and fine motor behavior. Tg344-AD (Tg; n=12: 6 males, 6 females) and age-matched wild-type (WT) (n=12: 6 males, 6 females) rats were assessed longitudinally at

6, 12, 18, and 24 months. Analysis is ongoing for 18 and 24 months of age. At 12 months, Tg rats showed significant ($p = 0.027$) spatial deficits compared to WT rats in the Morris Water Maze (MWM), measured by increased swim distance to platform indicating worse performance. Cognitive flexibility, measured by placing the platform in the opposite chamber, was reduced at 12 months of age ($U = 1610.0$, $p = 0.010$) in Tg rats. In the fine motor task (Melick et al., 2025), Tg rats demonstrated a deficit in task performance at 6 ($p = 1.77 \times 10^{-5}$) and 12 months ($p = 1.57 \times 10^{-5}$) of age, measured by the proportion of successful attempts over total attempts. Behavior results thus demonstrate that the fine motor task is an earlier predictor of disease progression compared to the MWM, a cognitive task.

To understand how changes in behavior could be a result of neural disruptions, histology was performed on brain tissue at 10 months of age in a subset of animals (n=3 per genotype). Tg rats alone showed significantly elevated plaque burden in CA1 ($p = 0.0047$), motor cortex ($p < 0.001$), and molecular layer of the cerebellum ($p = 0.025$) compared to WT. Interestingly no differences were found in microglia, astrocytes, MBP, or MAP2, but PNN intensity was reduced in the cerebellar dentate nucleus. To see if changes in PNNs could influence neural complexity, Golgi-cox staining and sholl analysis were performed. In a subset of animals In the motor cortex, WT rats had increased intersections ($p = 0.001$) compared to Tg rats, demonstrating reduced neural complexity due to increasing pathology. Thus, we found that 10-12 months is when larger changes in cognition and fine motor behavior are found, which correlates with increasing plaque burden, impaired PNNs, and reduced neural complexity.

Long-term outcomes: Human pathology samples will undergo continued analysis. Behavior data from animal studies will be completed at 18 and 24 months of age. Brain tissue collected at 24 months of age will undergo histological analysis. Changes in behavior and neural markers across the lifespan will be analyzed in the TgF344-AD rats, with a focus on sex-specific differences. This project is expected to produce a minimum of 5 manuscripts with two currently in writing. Data will be presented as a poster in Fall 2026 at the Society for Neuroscience in Washington, D.C. and the AAC conference in Tucson. I have also been invited to present an oral presentation at the Cerebellar Gordon Research Conference in August 2027.

Challenges encountered: Perineuronal nets are not commonly imaged in human brain tissue and finding reliable antibodies was an initial challenge. In addition, the health of the aging TgF344-AD rats had to be carefully monitored as animals could deteriorate quickly after reaching 17 months of age.

Future grant applicants and collaborations: Work from this grant supported pilot data for a number of grants submitted this year, including to the National Institutes of Health, National Science Foundation, Alzheimer's Association, and the Arizona Biomedical Research Centre (ABRC). In addition, a new R01 will be submitted to the upcoming cerebellum and Alzheimer’s disease funding announcement.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Leveraging Vision-Language Models for Automated Retinal Biomarker Analysis in Preclinical Alzheimer's Disease. Yalin Wang, PhD, Oana M Dumitrascu, MD, MSc, FAHA, FAAN, Yi Su, PhD. Arizona State University; Mayo Clinic; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Project Description:

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with a long preclinical phase marked by silent vascular and pathological changes. The retina, sharing origins and physiology with the brain, offers a non-invasive window into early AD. Retinal vascular dysfunction—such as reduced fractal dimension and vessel complexity—has been linked to cerebral amyloid burden and cognitive decline, particularly in APOE4 carriers, a key genetic risk group. However, existing fractal analysis tools are slow and not clinically scalable. We propose RetinalGPT, a vision-language model that automates and accelerates retinal vascular fractal analysis through biomedical knowledge integration and domain-specific instruction tuning. Applied to cognitively normal individuals with known APOE genotype and amyloid-PET status, RetinalGPT will enable scalable investigation of APOE4-related microvascular changes in preclinical AD.

Specific Aim(s):

Develop AI-assisted retinal vascular analysis methods to identify preclinical AD-related microvascular alterations in APOE4 carriers. Hypothesis: RetinalGPT will enable accurate and efficient measurement of retinal fractal dimensions that correlate with amyloid burden, cognitive performance, and neurovascular integrity, offering a clinically scalable, non-invasive biomarker for early AD risk stratification.

(a) Apply RetinalGPT to compute fractal dimensions and vascular morphological features from color fundus photography in cognitively normal individuals with known APOE genotypes and amyloid-PET status, to determine the impact of APOE4 and amyloid positivity on retinal vascular complexity. **(b)** Assess the relationship between RetinalGPT-derived fractal measures and cognitive function, hypothesizing that lower retinal vascular complexity is associated with reduced delayed memory performance in APOE4 carriers.

Background and Significance:

AD is a progressive neurodegenerative disorder with a prolonged preclinical phase, during which neuropathological changes such as amyloid-β accumulation and neurovascular dysfunction gradually emerge before clinical symptoms appear. Recent evidence suggests that the retina, as an extension of the central nervous system, undergoes microvascular changes that not only mirror but may precede cerebral pathology[1]. Alterations in retinal vascular features—such as reduced fractal dimension, increased tortuosity, and diminished branching complexity—have been linked to amyloid burden[2], cognitive decline[3,4], and cerebral small vessel disease[5,6]. These changes are particularly evident in individuals carrying the APOE4 allele[7], the strongest genetic risk factor for late-onset AD[3], and may reflect early microvascular compromise related to blood-brain and blood-retinal barrier dysfunction[1]. Quantifying such vascular features offers a promising avenue for developing non-invasive biomarkers for early AD detection. Fractal analysis provides a robust metric for vascular complexity[8–10], but its clinical utility is currently limited by computational demands and lack of scalable tools. To address this, we employ a larage vision-language foundation model to automate and standardize vascular feature extraction from fundus images, enabling efficient large-scale analysis across individuals with different genetic and imaging profiles. This approach supports a broader investigation into the relationship between retinal vascular morphology, genetic risk (e.g., APOE4 status)[11–14], cognitive function, and neuroimaging markers such as amyloid-PET and MRI-derived metrics of white matter integrity. By establishing these associations

in cognitively normal individuals, this work aims to evaluate the utility of retinal vascular complexity as an early, scalable, and clinically meaningful biomarker for AD risk stratification.

Preliminary Data, Experimental Design and Methods:
We developed RetinalGPT as a large vision-language model for automated analysis of color fundus photography (CFP), supported by more than 42,000 fundus images from public datasets and quantitative vascular features extracted with AutoMorph and RBAD, including fractal dimension, tortuosity, vessel density, vessel width, and branching angle. RetinalGPT was trained through two-stage instruction tuning, combining CLIP-LLaMA image-text alignment with Mixup-based retinal Q&A and biomedical knowledge tuning, and is organized as a modular multi-agent system for scalable feature extraction, biomarker stratification, and cohort-level inference. In preliminary evaluation, predicted vascular measures closely matched AutoMorph and RBAD ground truth across retinal zones, with an average difference of +/-0.073, supporting its reliability for ophthalmic vascular assessment. In the proposed study, we will apply RetinalGPT to the Mayo Clinic AZ APOE cohort of 330 cognitively unimpaired participants, including 100 amyloid-PET-positive preclinical AD cases and 230 amyloid-PET-negative controls aged 50-90 years with CFP, APOE genotype, amyloid-PET, MRI, and cognitive testing, to quantify retinal fractal dimensions and vascular morphology. We will test whether RetinalGPT-assisted fractal analysis detects APOE4- and amyloid-associated microvascular dysfunction and whether reduced retinal vascular complexity correlates with delayed memory performance, cerebral amyloid burden, white matter hyperintensity, cerebral blood flow, and other neurovascular MRI markers in an APOE4 allelic dose-dependent fashion.

Proposed One-Year and Long-Term Outcomes
We expect to publish 3-4 joint papers during this funding period. With the preliminary results accumulated from this project, we plan to submit an NIA R01 grant in August 2025.

Year-End Progress Summary:
R01 Deep Learning-Based Retinal Imaging Screening Tool for Preclinical Alzheimer's Disease. During this reporting period, we submitted an NIA R01 application. The application builds directly on the AAC-funded retinal biomarker work by proposing an end-to-end, clinic-friendly platform for non-invasive preclinical AD screening with non-mydriatic color fundus photography. The proposed system will develop Topology-Preserving Optimal Transport with domain adaptation (TPOT-DA) to improve low-quality retinal images while preserving vascular structure, design nn-MobileNet++ for automated AD-related retinal biomarker detection, and test whether CFP alone, blood-based biomarkers alone, and integrated CFP+BBBM models can predict PET- and BBBM-defined amyloid positivity. The project leverages UK Biobank, CLSA, Mayo AD and preclinical AD cohorts, and the rural MindCrowd MobileLab cohort to evaluate generalizability in both research and real-world point-of-care settings. The grant was reviewed in an NIH study section meeting in January 2026 and received a 5th percentile score, providing strong external validation of the scientific premise, preliminary data, and translational significance of this AAC-supported research direction.

R01 CRCNS Integrating MRI and Blood Biomarkers for Amyloid Ambiguity and Progression. We submitted the CRCNS R01 application in May 2026. This project proposes a geometric deep learning framework that integrates blood-based biomarkers with structural MRI to resolve amyloid ambiguity in the 20-40% of individuals whose BBBM results fall in intermediate or discordant ranges. The work will develop BBBM + sMRI tetrahedral transformer systems to estimate global and regional amyloid burden, conditional generative models that create individualized digital twins for forecasting longitudinal brain atrophy, and validation studies across late-onset AD, autosomal-dominant AD, and multiethnic cohorts. By releasing

open-source software, the project aims to support scalable, non-invasive AD risk assessment, precision monitoring, and clinical-trial enrichment. The grant was reviewed in an NIH study section meeting in March 2026 and received an impact score of 26.

LLaDA-MedV: Exploring Large Language Diffusion Models for Biomedical Image Understanding. This work introduced LLaDA-MedV, the first large language diffusion model adapted for biomedical image understanding through visual instruction tuning. Unlike standard autoregressive biomedical vision-language models, LLaDA-MedV uses masked diffusion to predict and refine multiple response tokens in parallel, enabling fixed-length answers with more direct control over response length. Training included biomedical semantic alignment, end-to-end visual instruction tuning, and dataset-specific fine-tuning on VQA-RAD, SLAKE, and PathVQA. Across open-ended biomedical conversation tasks, LLaDA-MedV achieved the best overall score among evaluated models, outperforming LLaVA-Med and LLaDA-V. Closed-form biomedical VQA accuracy was 84.93% on VQA-RAD, 92.31% on SLAKE, and 95.15% on PathVQA, setting the strongest closed-form results among the compared systems.

Talk Before You Retrieve: Agent-Led Discussions for Better RAG in Medical QA. This paper developed Discuss-RAG, a plug-and-play agent-led framework for improving retrieval-augmented generation in medical question answering. The work addresses two common weaknesses of medical RAG systems: retrieval based only on surface similarity and direct use of retrieved snippets without sufficient clinical verification. Discuss-RAG treats retrieval as a reasoning process rather than a one-step search operation. For each medical query, a recruiter assembles specialized medical agents, a summarizer moderates multi-turn brainstorming, and a verifier distills the discussion into a concise, retrieval-ready summary that captures the key medical concepts and reasoning steps. After retrieval, a decision-making agent filters irrelevant or incoherent snippets before answer generation. In a fair comparison using the same medical textbook corpus, MedCPT retriever, and GPT-3.5 backbone as MedRAG, Discuss-RAG consistently improved answer accuracy across four medical QA benchmarks, with gains of 5.70% on MMLU-Med, 4.40% on MedQA-US, 16.67% on BioASQ, and 12.20% on PubMedQA. These results show that agent-guided retrieval and post-retrieval verification can make medical QA systems more reliable, interpretable, and clinically grounded.

OphIn-500K: Curating Web-Scale Visual Instructions for Scaling Ophthalmic Multimodal Large Language Models. This work created OphIn-Engine, an automated pipeline for converting open-access ophthalmology videos into high-quality multimodal instruction data, and used it to build OphIn-500K, a web-scale ophthalmology instruction dataset with 536,132 instruction instances from 151,430 unique images and 29,465 video clips. It spans CFP, OCT, and ultra-widefield fundus imaging, includes visual question answering, multi-turn clinical conversations, and chain-of-thought reasoning, and covers more than 1,000 retinal conditions and approximately 800 anatomical features. OphIn-Engine combines frame filtering, transcription, de-identification, instruction synthesis, and post-verification to draw visually novel image-text pairs from real-world ophthalmic video sources. Using OphIn-500K, the authors trained OphIn-VL, an ophthalmology-specific multimodal large language model based on a Qwen-3.5-9B language backbone with efficient LoRA fine-tuning while keeping the vision encoder frozen. The model substantially outperformed general medical, ophthalmology-specific, and general-domain baselines on the OphIn-VQA test split, achieving 97.33% on Yes/No questions, 54.71% on What questions, 53.75% on Where questions, and 70.00% average LLM-judge accuracy. The study provides a scalable path for moving ophthalmic AI beyond recycled public benchmarks toward visually novel, clinically grounded conversational systems that can support future retinal disease screening, education, and decision-support research.

BANNER ALZHEIMER'S INSTITUTE - PHOENIX
PROJECT PROGRESS REPORTS

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Alzheimer's Prevention Initiative. Robert Alexander, MD, Eric M. Reiman, MD, Pierre N. Tariot, MD, Jessica B. Langbaum, PhD, Jeremy Pruzin, MD, Nicholas Ashton, PhD, Alireza Atri, MD, PhD, Valentina Ghisays, PhD. Banner Alzheimer's Institute; Banner Sun Health Research Institute; University of Arizona; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

1. To support plans for securing regulatory approval of and implementing widespread accessibility to effective secondary prevention therapies within the next three years, and primary prevention therapies within five years as outlined in the *Lancet Neurology* article.
2. To support analyses of data and biological samples from observational studies to inform the design and outcomes measures for use in future primary and secondary prevention trials in at-risk individuals.
3. To support efforts for our trial of a gamma secretase modulator and a plaque clearing antibody in the PSEN1 E280A kindred in Colombia, including efforts for infrastructure support and data collection and analyses of the ancillary API Colombian Registry.
4. To support analyses of the results of the API eSMARTER trial, a randomized controlled trial of two different risk disclosure delivery models (self-directed disclosure through an interactive online portal vs. healthcare provider mediated disclosure) to return AD genetic and biomarker results to approximately 600 individuals enrolled in GeneMatch.
5. To continue efforts partially supported by NIH funding to improve the infrastructure of web-based registries for both members and researchers.
6. To support efforts to plan for and secure funding for other API led preclinical treatment trials programs/surrogate marker development programs in cognitively unimpaired individuals who are at risk for ADAD or LOAD.

Background and Significance:

Alzheimer's disease (AD) is the most common form of dementia. This devastating illness takes a significant toll on clinically affected persons and family caregivers and will take an overwhelming financial toll on society. Results from observational studies suggest that the pathophysiological process of AD begins years, if not decades, before the diagnosis of clinical dementia. In 2023, the FDA granted full (traditional) approval to lecanemab, the first disease modifying treatment for early people with early AD. This was followed by the approval of donanemab in 2024, another anti-amyloid antibody. While encouraging, the clinical benefits of these treatments in people with cognitive symptoms of AD are modest. It has been suggested that at least some therapeutic interventions, particularly those that target amyloid pathology, need to be started before the clinical onset of AD, when there is already extensive neuropathology, in order to exert their maximum effects. Indeed, secondary prevention therapies have the potential to avert further disease progression and to stop or delay cognitive impairment in people with biomarker evidence of the disease. Primary prevention therapies have the potential to avert the disease itself in people without cognitive impairment. Based on developments from the past 3 years, there is a realistic chance to develop, secure regulatory approval of, and implement widespread accessibility to effective preventive therapies in the next few years. We believe that intravenously administered anti-amyloid antibodies for secondary prevention of AD can be available within 3 years, and subcutaneously self-administered therapies soon thereafter. We also think that subcutaneous antibody therapies for primary prevention can be developed within 5 years. At the same time, there have been exciting developments in our ability to detect AD pathology in blood. These promising blood-based biomarkers make it possible to screen large numbers of individuals for enrolment into clinical trial programs and, once a treatment is

approved, use such tests to identify who would benefit from treatment with a prevention therapy. These developments require researchers and clinicians to implement scalable methods for disclosing AD genetic and biomarker test results to participants and patients.

Preliminary Data, Experimental Design and Methods:

We and our colleagues demonstrated the promise of plasma p-tau217 in the diagnosis and unusually early detection of AD, including the onset of measurements p-tau217 elevations about two decades before the ADAD mutation carriers' estimated age at MCI onset[1]. We analyzed baseline, 2-year, and 5-year amyloid PET scans from 161 cognitively unimpaired PSEN1 E280A carriers (ages 30–56) enrolled in the Alzheimer's Prevention Initiative (API) ADAD Colombia Trial (NCT01998841). applied to estimate the age of onset of amyloid positivity (using centiloid threshold of 20 for positivity). The estimated age of amyloid onset was 26.1 years (SD ±7.89, range 1-54) and estimates were normally distributed. Although there were no sex differences, APOE4-positive mutation carriers had an EOA about 3 years younger than APOE4-negative mutation carriers ($p = 0.03$). CDR-SB trajectories revealed substantial variability in clinical symptom progression, further emphasizing the heterogeneity in disease onset and progression.

In addition, we demonstrated an association between two copies of the rare APOE3 Christchurch variant in a PSEN1 E280A mutation carrier who was resistant to the clinical onset of ADAD and performed of related experimental studies to suggest the mechanism by which APOE, its variants and future APOE-related treatments might exert their therapeutic effects[2], we demonstrated that two copies of the APOE2 allele are also associated with an exceptionally low risk of neuropathologically confirmed AD dementia, found that APOE and its common variants have a greater impact on AD dementia risk than previously thought, provided further support for the development of APOE-modifying drug and gene therapies in a case-control study of >5,000 well characterized brain donors[3]. Our "Paving a Path to Accessibility of the First Effective Secondary and Primary Alzheimer's Prevention Drug Therapies" symposium was held in February 2025 in Arlington, VA, and brought together leading academic and industry researchers, regulators, payers, policy makers, patient and family advocates, and other stakeholders to consider what scientific data or strategies are needed to support the traditional or accelerated approval of the first effective secondary and primary AD prevention therapies.

Proposed One-Year and Long-Term Outcomes:

For Aim 1, we will submit a policy paper, inclusive of though leaders who participated in our Symposium described above, to Lancet Neurology in Summer/Fall 2025. Our long-term outcomes are to detail what is needed to find and support the accessibility of secondary and primary prevention trials by some time in 2026 and 2028, respectively. For Aim 2, we will work with API leaders and partners to obtain and analyze data and samples from observational studies to inform the trial population, design and outcome measures for use in future primary and secondary prevention trials in at-risk individuals. For Aim 3, we anticipate beginning enrollment in the new API ADAD Colombia clinical trial in Q1 of 2026. For Aim 4, we anticipate completing enrollment by summer 2025 and nearly complete with all data collection during the funding period. As a long-term outcome, this platform is adaptable and will be leveraged by a number of different programs for future use. For Aim 5, we will complete the overhaul of the endALZnow.org website and implement text messaging and other new features by mid-2025, improving the experience for Registry members and researchers. The improved infrastructure will have a positive effect and likely increase enrolment and engagement of members and usage of the programs by researchers. For Aim 6, we will continue to engage in discussions with partners and funders in support of future API trials. For all API programs, we will continue to seek additional external, non-state funding from NIH, industry and philanthropic organizations to support our efforts to conduct trials in at-risk populations.

Year End Progress Summary:

For Aim 1, we published our policy view, "A Path to Preventing Cognitive Impairment due to Alzheimer's Disease: Initiatives Beginning in the USA" in Lancet Neurology[OBJ][OBJ] In the policy view, we discuss the current landscape of preclinical and primary prevention treatments for Alzheimer's disease, asses the challenges and opportunities that trials of these drug treatments will bring, and consider the blood tests, cognitive assessments, and post-marketing strategies needed to enable the approval, affordability, health-care insurance coverage, and equitable use. Our recommendations are intended for consideration in the USA, and relevant refinement in other countries.

For Aim 2, we have leveraged several NIH grant and other funding sources to acquire and analyze longitudinal data from several prospective cohort studies, clinical trials, and a growing number of population-based studies to: a) inform the size and design of 3- to 4-year primary prevention trials using amyloid PET and plasma pTau217 as potential surrogate biomarker endpoints; b) work with industry colleagues on the design of the first two primary prevention trials of treatments to avert the onset of amyloid plaques, which could be initiated within a year if the first secondary prevention therapy is established to substantially prevent the onset of MCI and dementia due to AD; and c) characterize the clinical, cognitive, amyloid and tau PET, CSF biomarker, and plasma biomarker trajectories in placebo-treated ADAD mutation carriers and non-carriers from our original API ADAD Colombia Trial[5],

Beyond this particular aim, we continue to acquire and analyze data from prospective cohort and population-based studies to estimate a cognitively unimpaired person's short, intermediate and long-term risk of progression to MCI and dementia due to AD based on his or her plasma p-Tau 217 measurements of amyloid plaque deposition, alone or in conjunction with emerging plasma eMTBR-243 measurements of plaque-related tau tangle deposition using an assay developed this year in the Ashton lab, APOE genetic test results, age, education, and sex—and develop a user-friendly on-line calculator for patients and providers to estimate a person's risk without treatment, such that it will inform the appropriate use of future preventative drug therapies and existing health-promoting lifestyle interventions and support the coverage of preventative screening blood tests as soon as the first preventative drug therapy becomes available. We have posted a medRxiv preprint evaluating the prognostic value of plasma brain-derived pTau217 and total plasma pTau217 for predicting amyloid PET and clinical progression in cognitively unimpaired ADNI participants[6], acquired data from the population-based Framingham Heart Study (FHS) to provide more representative estimates, and are in the process of securing funds to acquire pTau217 and eMTBR-243 data from the large, nationally representative Health and Retirement Study (HRS).

We are using this and other information to help policy makers and other stakeholders consider what is needed to find and support the approval, appropriate and equitable use, and coverage of the first effective secondary and primary prevention therapies, and the preventative screening blood and cognitive tests needed to inform their use. For Aim 3, we made substantial progress in securing contracts, agreements, and regulatory approvals required to commence enrollment of participants into our NIH-funded trial of a gamma secretase modulator and a plaque clearing antibody in the PSEN1 E280A kindred in Colombia, including efforts for infrastructure support and data collection and analyses of the ancillary API Colombian Registry. The study will test the efficacy (as measured by amyloid PET) of Lilly's anti-amyloid antibody, donanemab, in ADAD. The study will also explore various ways to maintain low brain amyloid levels using donanemab, a novel gamma secretase modulator from Roche, RG6289, or the combination of the two drugs. While this study will be performed in Colombia, we believe it will provide important scientific information for both ADAD and late-onset Alzheimer's Disease patients in the United States. We received Colombian regulatory approval on January 16, 2026, and the Investigator Meeting (IM) was held on February 25-26, 2026, in Medellín. This meeting included protocol training, review of site and medical monitoring plans,

safety reporting with an emphasis on ARIA training, and trial specific vendor overviews for labs, cognitive assessments, IRT, ECG, and imaging centers. Our Site Initiation Meeting was completed on May 9, 2026, and the Clinical Trial Agreement between our CRO and the University of Antioquia was finalized on June 26, 2026. All study start-up activities, including finalization of local and specialty lab contracts and study manuals, provision of study equipment to trial site, qualification of MRI and PET scanners, training and provision of study materials to the site, and establishment of the study's electronic databases have been completed, and the first screening of a study participant was completed July 2, 2026.

For Aim 4, the eSMARTER trial data collected was completed in November 2025; data analyses are ongoing. A manuscript describing the eSMARTER study design was published in *Alzheimer's & Dementia: Translational Research and Clinical Interventions* in November 2025.[7] Topline results will be presented at AAIC 2026; a manuscript is being prepared for submission to *JAMA* Neurology. High-level results from eSMARTER are below.

Participant demographics. eSMARTER enrolled 681 adults from all lower 48 US states and the District of Columbia. 440 participants from were randomized to digital return and 218 to healthcare provider return of results. The mean age of participants was 68 years and 67.5% were female, 90.5% were White, 77.9% had ≥4 years of university-level education,10.2% were APOE4 homozygotes, 57.8% were heterozygotes and 32.1% were noncarriers. 47% of participants were classified as pTau217 negative, 31% intermediate, and 22% positive.

Topline APOE Disclosure results. In primary intention-to-treat analyses, non-inferiority **was met** for short-term (change from baseline at 2-7 days after disclosure) primary outcomes including knowledge, anxiety and disease-specific distress. Non-inferiority was also met for these outcomes (change from baseline at 6 weeks after disclosure and at 6 months after disclosure). Analyses of secondary patient-reported outcomes, outcomes by APOE genotype and per-protocol, as-treated and moderator analyses are ongoing.

Topline pTau217 Exploratory results. There were no statistical differences on measures of pTau217 knowledge, anxiety, and disease-specific distress between the and clinician-led and eHealth self-directed arms. Analyses of other secondary patient-reported outcomes, outcomes by pTau-217, and moderator analyses are ongoing.

For Aim 5, we continued to apply learnings from our review of the participant registry market and data from our other NIA-funded grants to guide the redesign of the website. During the past year, the site was moved from Sitecore to Salesforce. The "Find a Study" page redesign went live. We've worked with a UI/UX consultant to redesign the rest of the website with an anticipated go live in late Q3 to Q4 2026. In 2026, we tested our evidence-based recruitment messages and concluded that (1) for both registries, evidence-based messages outperformed standard messages in conversion rate (joining the registry); and (2) evidence-based messages developed for social media were more effective than standard messages at enrolling adults at high risk for ADRD. These data provide support that the evidence-based messages designed to persuade those at high risk and currently under-enrolled in registries were more effective than the standard messages, but low enrollment numbers in general suggest that other recruitment methods are necessary. We conducted a feasibility study with the same evidence-based ads to test whether Electronic Health Record (EHR) patient portals could be a recruitment method for registries and, ultimately, clinical studies. Our findings suggest the evidence-based messages developed for social media were efficient and effective at enrolling high-risk adults into a registry via EHRs with early data suggesting EHRs are more effective than social media. We will be presenting the EHR data at AAIC 2026. In April 2026, we submitted a new NIH grant application to support scaling up recruitment for registries and to develop evidence-based messages for direct enrollment into clinical studies that can be disseminated through EHRs.

For Aim 6, we have contributed to numerous discussions with industry, philanthropic and other strategic partners to plan for and secure funding for other API led preclinical treatment trials programs/surrogate marker development programs in cognitively unimpaired individuals who are at risk for ADAD or LOAD. In June 2026, we submitted a significant NIH grant application proposing the necessary first step to develop the trial evidence that Bacillus Calmette–Guérin (BCG) immunotherapy can delay the onset of memory and thinking problems characteristic of mild cognitive impairment (MCI) and AD dementia. If the biomarker and/or clinical results of the first stage of the trial were positive, this could result in FDA consultation to consider accelerated approval and also justify bringing the trial to completion with continued funding; positive clinical results of the complete trial would establish that a safe, repurposed, low-cost, and readily scalable therapy with simple adherence can meaningfully lower the risk of developing MCI and dementia due to AD for older adults across the US.

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ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

User testing, perceptions, understanding, and satisfaction with learning pTau-217 results.
Claire Erickson, PhD, MPA, Nicholas Ashton, PhD, Jessica Langbaum, PhD. Banner Alzheimer's Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:
The *overall objective* of this proposal is to develop materials for return of pTau-217 results and characterize participant perceptions, understanding, and satisfaction after learning their plasma pTau-217 results by leveraging the GeneMatch registry and two ongoing studies (eSMARTER and Draw-10) being conducted within the Alzheimer's Prevention Initiative (API) at Banner Alzheimer's Institute. These pilot data will be the foundation for future grant applications. To address this objective, I will pursue the following *specific aims*:

1) Aim 1: Develop, test, and refine participant-facing pTau-217 materials for education and return of results. *Approach:* Materials will initially be developed in collaboration with experts in blood Alzheimer's disease (AD) biomarkers. User testing of the pTau-217 education content and disclosure content will be conducted with GeneMatch participants. Following user testing, materials will be further refined to improve understandability.
   Research Question 1: How can information about pTau-217 testing and results be effectively communicated to participants?
2) Aim 2: Characterize perceptions about personal AD risk, utilization of pTau-217 results, and satisfaction with the disclosure process. *Approach:* Quantitative analysis of surveys administered to participants who learned their pTau-217 results as a part of the Evaluation of Self-Mediated Alternatives for Risk Testing Education and Return of Results (eSMARTER) and/or Draw-10 studies.
   Research Question 1: How do participants perceive their risk of AD after learning their pTau-217 results? *Hypothesis:* Participants who learn a positive pTau-217 result will rate their AD risk as higher than those who learn an intermediate or negative result.
   Research Question 2: What actions do participants take after learning their pTau-217 results (e.g., sharing with others, planning for the future, making lifestyle changes, seeking out medical appointments, etc.)? *Hypothesis:* Participants who learn an intermediate or positive pTau-217 result will report more actions post-disclosure than those who learn a negative result.

Background and Significance:
Returning Alzheimer's disease (AD) biomarker is becoming more common with the availability of disease-modifying therapies. Prior studies demonstrate sharing *APOE* genetic results and amyloid neuroimaging results can be done in ways that ensure participant understanding and minimize psychological distress[1]. The development of AD blood biomarkers offers a new avenue of AD biomarker disclosure. Though not yet part of routine care, AD blood biomarkers, namely pTau-217, are poised for broad use in diagnosis and management[2] and are already used in clinical trials to determine participant eligibility[3]. To date, current practices for returning blood biomarker results focus on implications for trial eligibility, as opposed to risks for AD or treatment side effects. The growing utility of AD blood biomarkers thus requires further development of methods to communicate results.

Further, advancements in blood biomarkers are reducing barriers to testing by making tests lower cost and less invasive. Increased accessibility to testing means more people are likely to receive AD biomarker results in the coming future. The added context of the 21st Century Cures Act, which mandates immediate return of most medical tests, coupled with the shortage of genetic counselors and dementia specialists[4,5], heightens the *critical need* to return results in ways that minimize healthcare system burden[2].

This study will proactively develop materials for returning pTau-217 results and gather needed data to characterize participant perceptions, understanding, and satisfaction with learning pTau-217 results. Overall, this project will provide novel materials for and data about disclosing pTau-217 results and aid the development of remote disclosure processes for AD blood biomarkers for use in research and clinical settings. The proposed study is innovative in its focus on participant experiences learning pTau-217 results. Other studies have investigated the participant experience learning *APOE* genetic information and/or amyloid neuroimaging results, but few have focused on pTau-217 results. The proposed research is innovative in its approach to returning results, relying on eHealth strategies for communicating results. This approach will help with the development of scalable disclosure practices by triaging clinician time and providing access to a broader population who do not or cannot travel to academic medical centers.

Preliminary Data, Experimental Design and Methods:

Participants in Aim 1 will be drawn from GeneMatch, which maintains a registry of older adults who live in the United States and do not report a diagnosis of cognitive impairment. The function of GeneMatch is to connect older adults interested in participating in research with relevant studies.

Participants in Aim 2 will be drawn from eSMARTER and Draw-10; both are ongoing studies. The Evaluation of Self-Mediated Alternatives for Risk Testing Education and Return of Results (eSMARTER) is a decentralized, randomized trial to evaluate self-directed, scalable eHealth platforms for communicating *APOE* and plasma pTau-217 results. pTau-217 disclosure will occur approximately six months post-*APOE* disclosure. Across the US, approximately 650 adults aged 60-80 are enrolled (#NCT06459583). The sample includes around 400 *APOE4* carriers and 250 non-carriers. Draw-10 is an observational research study exploring fluctuations in blood biomarkers serially drawn over 10 weeks. The study will enroll approximately 100 participants aged 50-80 years old (currently 47 participants are enrolled). Participants will have the option to learn their overall pTau-217 result following completion of all blood analysis.

The protocols and materials for returning pTau-217 results were developed based on expertise and data from other studies and programs, including the Generation Program trials, CONNECT4, and the Alzheimer's Disease Neuroimaging Initiative.

Experimental Designs and Methods

Sampling and Data Collection

Aim 1: GeneMatch registrants aged 60-80 who live in the US and do not have a self-reported diagnosis of cognitive impairment will be identified by GeneMatch and invited to participate. Participants who enrolled in the previous studies Generation and eSMARTER will be excluded. Enrolled participants will engage in user testing of our web-portal intervention education content (n=15) and disclosure content (n=15). User testing will be guided by the usability engineering concept, which emphasizes an iterative design approach, testing and observing users with the prototype will ensure the relevance and usefulness of the resulting products[6]. Participants will be asked a series of assessment questions to understand the extent to which the content is useful, personally relevant, easily interpreted, accessible, and salient.

Aim 2: All participants enrolled in eSMARTER and Draw-10 who learn their pTau-217 result (n=TBD) will be contacted to complete a REDCap survey related to their perceptions about personal AD risk, utilization of pTau-217 results, and satisfaction with the disclosure process.

Proposed Analysis

*User testing interview*s: Following review of pTau-217 study materials, participant feedback will be collected utilizing a series of questions. Notes will be taken during the interviews to collect feedback. Participant feedback will be used to inform the refinement of the education and disclosure content.

Surveys: Data collected from REDCap will be analyzed using Excel and R Studio. Descriptive statistics will be utilized, as well as T-tests to make comparison between participants who learn negative, intermediate, and positive pTau-217 results.

Proposed One-Year and Long-Term Outcomes: By the end of the one year award period, I plan to present results at the annual AAC meeting and begin writing a first-author manuscript. Long-term, results from this study will be used to inform return of results practices within the Arizona ADRC clinical core. I plan to utilize findings from this work in the development of future grant applications, including for a 2026/27 NIH R03 application to continue my work on biomarker disclosure. I plan to also use the data collected herein for 2026/27 submissions for the Alzheimer's Association Research Fellowship (AARF) and National Alzheimer's Coordinating Center (NACC) New Investigator Award Program.

Year End Progress Summary:

This project focused on developing and evaluating participant-centered educational materials and return-of-results procedures for plasma pTau-217, an emerging blood biomarker for Alzheimer's disease. As blood-based biomarkers become increasingly integrated into research and clinical care, there is a critical need for educational resources and scalable disclosure methods that are understandable, acceptable, and support informed decision-making. During the reporting period, substantial progress was made toward both specific aims.

Aim 1: Develop, test, and refine participant-facing pTau-217 materials for education and return of results

We developed participant-facing educational and disclosure materials to support communication of plasma pTau-217 results and systematically evaluated these materials using the U.S. Department of Health and Human Services Patient Education Materials Assessment Tool (PEMAT) for Printable Materials. The PEMAT assesses both understandability (17 items) and actionability (5 items), with higher scores indicating higher quality educational materials.

I interviewed 20 participants. Their average age was 69.7±7.5 years, 60% (n=12) were female, 90% (n=18) self-identified as non-Hispanic White and 10% (n=2) identified as Hispanic White. 90% of participants (n=18) had a bachelor's degree or higher and over half (65%, n=13) had a biological relative who had dementia. Overall, participants rated the materials highly. Understandability scores ranged from 70.5% to 100%, with an average score of 89% (±9%) and a median score of 88%. Actionability scores ranged from 60% to 100%, with an average of 90% (±12%) and a median of 100%.

The evaluation also identified specific opportunities for refinement. For understandability, participants most frequently recommended improving organization by breaking information into shorter sections, providing an executive summary, increasing the use of visual cues (e.g., bolding, bullets, highlighting), and incorporating additional graphics to enhance comprehension. For actionability, participants suggested adding more visual aids to support recommended actions and presenting action steps in a more explicit, stepwise format. Qualitative feedback similarly emphasized reducing text-heavy slides, expanding the use of graphics, incorporating an executive summary, and making minor wording and grammatical revisions. Importantly, participants consistently reported that the materials were informative, easy to understand, and particularly valued the sections discussing practical considerations surrounding pTau-217 testing.

Based on these findings, the educational materials are being refined to improve readability, visual presentation, and usability, resulting in participant-informed resources that are well-positioned for broader implementation.

Aim 2: Characterize perceptions about personal AD risk, utilization of pTau-217 results, and satisfaction with the disclosure process

This aim is being addressed within the eSMARTER randomized, decentralized clinical trial evaluating scalable approaches for returning APOE genotype and plasma pTau-217 results. During the reporting period, 505 participants from all 48 contiguous United States and the District of Columbia were enrolled and randomized to receive results either through a self-directed eHealth platform or clinician-led telehealth disclosure. Participants represented a broad range of pTau-217 results, with 47% testing negative, 31% intermediate, and 22% positive.

Primary analyses utilizing the eSMARTER data demonstrated that participant-directed eHealth disclosure was comparable to clinician-led telehealth disclosure. There were no significant between-group differences in blood biomarker knowledge immediately following disclosure or four weeks later, nor were there significant differences in changes in general anxiety or Alzheimer's disease-specific distress across follow-up assessments. Participants also rated their satisfaction with receiving the results highly (mean: 4.4/5). These findings provide strong preliminary evidence that participant-directed eHealth approaches can safely and effectively communicate pTau-217 results while reducing demands on specialized clinical personnel.

Analyses examining participants' perceptions of personal Alzheimer's disease risk, utilization of pTau-217 results, satisfaction with the disclosure process, and additional secondary outcomes are currently underway. These analyses will provide further insight into how individuals interpret and use blood biomarker results and will inform future implementation strategies for clinical practice.

Challenges Encountered

The primary challenge encountered during this reporting period relates to the participant sample used for user testing of the educational materials in Aim 1. Participants were recruited as a convenience sample from an ongoing longitudinal observational research cohort and, as such, were not nationally representative of the broader population who may ultimately receive pTau-217 testing. Although participants provided valuable and actionable feedback that led to meaningful improvements in the educational materials including recommendations to simplify content, improve visual presentation, and enhance organization, their familiarity with Alzheimer's disease research may have influenced their perspectives. Future work will seek input from individuals with less exposure to Alzheimer's disease research and from more diverse populations that better reflect those most likely to receive pTau-217 testing in clinical practice. Broader stakeholder engagement will be essential to ensure that the educational materials are accessible, understandable, and responsive to the needs of individuals from varied backgrounds and levels of health literacy.

Progress Toward Long-Term Outcomes:

This project has made substantial progress toward its long-term goal of developing scalable, evidence-based approaches for communicating Alzheimer's disease blood biomarker results. The refined educational materials provide a participant-informed framework for future clinical implementation, while the randomized trial findings support the feasibility of using self-directed eHealth platforms to return pTau-217 results without adversely affecting participant knowledge or psychological outcomes. Together, these findings contribute to the development of efficient, patient-centered models for blood biomarker disclosure that may help address anticipated workforce limitations as AD blood biomarker testing becomes more widely available.

The project has also strengthened ongoing collaborations among investigators studying Alzheimer's disease biomarkers, genetic counseling, patient education, and digital health implementation.

Dissemination, Collaborations, and Future Directions

Findings from this project have been disseminated through multiple research team meetings, the annual Arizona Alzheimer's Consortium Retreat, and the Alzheimer's Association International Conference (AAIC), where primary results from the randomized trial were presented. Results will also be presented at the fall 2026 Arizona Alzheimer's Consortium Scientific Meeting.

This project has fostered ongoing collaborations with Dr. Ashton and colleagues at the Banner Sun Health Research Institute, as well as collaborators at the University of Pennsylvania, including Drs. Jason Karlawish, Emily Largent, and Angela Bradbury. These multidisciplinary partnerships continue to advance research on participant-centered communication of Alzheimer's disease blood biomarker results and the development of scalable disclosure models.
Manuscripts describing the findings from Aim 2, including participant perceptions of Alzheimer's disease risk, utilization of pTau-217 results, satisfaction with the disclosure process, and additional patient-reported outcomes, are currently in preparation. Additional findings from this work are expected to be presented at the Clinical Trials on Alzheimer's Disease (CTAD) conference later in 2026.

Looking ahead, we will explore opportunities to implement and evaluate the refined pTau-217 educational materials within the Arizona ADRC and through additional collaborative studies. These efforts will further assess the generalizability and effectiveness of the materials across more diverse participant populations and clinical settings while informing future grant applications focused on implementation of Alzheimer's disease blood biomarker disclosure in research and clinical care. Grant applications for projects based on this work are currently underway and will be submitted to granting bodies such as the Alzheimer's Association and NIH.

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ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Alzheimer's Prevention Registry and its GeneMatch Program. Jessica B. Langbaum, PhD, Eric M. Reiman, MD, Robert Alexander, MD. Banner Alzheimer's Institute; Banner Sun Health Research Institute; Arizona State University; University of Arizona (Tucson); Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

1) Aim 1: To support partial continuation of the research previously supported by the terminated R01 grant, notably, measuring the impact of the evidence-based messages on enrollment into the Registry and its GeneMatch program and enrollees' subsequent willingness to participate in AD-related research studies and trials.
2) Aim 2: To support the preparation and submission of a new/renewal R01 grant to the NIH, likely focused on developing evidence-based messages that specifically addresses the beliefs, norms, and barriers to and facilitators for adults to join AD clinical studies for deployment in registries and electronic health records (EHRs).
3) Aim 3: To create an informed and engaged group Arizona-based members of the Alzheimer's Prevention Registry and its GeneMatch program by maintaining or increasing the open rate and unique click rates of emails sent to these individuals. These emails include our monthly Alzheimer's Prevention Bulletin newsletter and Arizona-based Events newsletter.
4) Aim 4: To maintain or increase the number of Arizona-based study opportunities available to Alzheimer's Prevention Registry members and GeneMatch participants, by offering recruitment assistance to new and early-stage Arizona ADRC and/or AAC researchers, or those who are established researchers collecting pilot or preliminary data to include in grant applications.

Background and Significance:

Over 6 million people in the United States (US) are living with Alzheimer's disease (AD), a number to projected to reach nearly 14 million by 2060 barring a medical breakthrough.[1] Interventions that delay onset even by 1 or 2 years would have a major public health impact.[2] However, current screening and enrollment processes are generally inefficient, contributing to the expense and duration of trials. Delayed or inefficient recruitment has scientific, financial, and ethical consequences.[3] Moreover, even when trials do meet their enrollment goals, individuals from understudied populations, particularly Black/African Americans and Hispanics/Latinos, are often underrepresented thus making it difficult to ensure that the findings of the study are generalizable.[4-6] In 2012, Banner Alzheimer's Institute (BAI) launched the Alzheimer's Prevention Registry (www.endALZnow.org) ("Registry") to help studies meet their enrollment goals in an efficient and timely manner.[7] The Registry launched its GeneMatch program in 2015. Individuals ages 50-90 who live in the United States and who self-report not having a diagnosis of cognitive impairment are eligible to enroll in GeneMatch. Upon enrollment into GeneMatch, participants are provided a cheek swab kit to provide a DNA sample for APOE genotyping, the results from which are used in part to help match to studies.[8] In 2019, BAI was awarded a R01 grant from the NIA (R01AG063954) that focused on how to effectively communicate the importance of joining the Registry and GeneMatch to currently under-enrolled and understudied populations, mainly Black and Hispanic adults and males. Using the theoretical framework of the Reasoned Action Approach (RAA), we identified key determinants and beliefs to perform our target behavior: joining an AD registry. We then used communication science principles and methods to incorporate these beliefs into evidence-based recruitment to drive enrollment into registries. This R01 grant was terminated abruptly, before the work could be completed and data analyzed, and while the

renewal grant was under review. It is important that we understand the impact of the evidence-based messages on enrollment into the Registry and its GeneMatch program and enrollees' subsequent willingness to participate in AD-related research studies and trials. The results from this effort will help accelerate enrollment into critically important AD-focused studies, particularly within Arizona.

Preliminary Data, Experimental Design and Methods:
To achieve Aim 1, we will analyze data from the terminated R01 to determine the impact of the evidence-based messages vs standard messages at increasing enrollment of men as well as Black and Hispanic adults into the registries. We will also analyze the data collected to examine registry enrollees' subsequent willingness to participate in AD-related research studies and trials. Lastly, we will prepare manuscripts summarizing the findings and submit these papers to journals for peer review.

To achieve Aim 2, we will work with colleagues from the terminated R01 grant to prepare and submit a new "renewal" R01 grant to the NIH, likely focused on developing evidence-based messages that specifically addresses the beliefs, norms, and barriers to and facilitators for adults to join AD clinical studies for deployment in registries and electronic health records (EHRs).

To achieve Aim 3, we will work with professional writers to develop relevant and engaging email newsletters for our members. We will track open rates and unique click rates of all emails, reporting metrics for all members and those who provide an Arizona-based zip code.

To achieve Aim 4, we will work with Arizona ADRC and AAC researchers to promote their studies to APR (and if appropriate, GeneMatch) members, with a particular emphasis on promoting pilot studies (for which the results will be used to support a future grant application) and studies led by new or early-stage investigators or researchers new to the AD field. We continue to offer a "scholarship" for these researchers to waive or substantially reduce the normal listing fees associated with promoting studies to APR / GeneMatch members. We will track the number of Arizona-based researchers who apply for this scholarship as well as the number of Arizona-based researchers and studies who use our program(s) to help meet their recruitment goals.

Proposed One-Year and Long-Term Outcomes:
Results from this effort will enable the team to partially complete an R01 project that was terminated early and summarize the findings for dissemination and serve as the basis for a grant application to the NIH. In addition, it will help support an engaged group of Arizona-based members of the Registry and its GeneMatch program who are interested in participating in research studies. In addition, we will measure the ability of the Registry and its GeneMatch program in helping Arizona-based studies meet their enrollment goals. These programs may serve as role models to the ADRC community as Centers across the US implement their local registry as required by the current Funding Announcement. Results will be submitted for publication in peer-reviewed journals and presented at scientific meetings. Lastly, data and findings will be used to inform future goals of the Registry. We will continue to seek additional external, non-state funding from NIH, industry and philanthropic organizations to support our efforts to expand the Registry and study the "science of recruitment" leveraging the Registry.

Year End Progress Summary:
Aim 1. We compared whether registry enrollment rates differed between people who were exposed to the standard vs the evidence-based messages used in Facebook ads. The evidence-based messages outperformed standard messages in conversion rate (joining the registry): APR standard messages 3.97% vs. evidence-based messages 11.59%; GM standard messages

4.00% vs. evidence-based messages 4.64%. Broken out by race and ethnicity, when pooled across all evidence-based messages vs. all standard messages, evidence–based messages outperformed standard messages across *all* registries for nearly *all* race/ethnic groups. The same was true for enrollment of men. **Conclusion:** Evidence-based messages developed for social media were more effective than standard messages. These data provide clear evidence that the evidence-based messages designed to persuade those at high risk and/or currently under-enrolled in registries were more effective than the standard messages, but low enrollment numbers in general suggest that other recruitment methods are necessary.
We then examined engagement of members to determine whether study participation differed between members who joined the registry through the standard and evidence-based Facebook ad messages. The proportion of members who joined via evidence-based messages and participated in a study (6.24%) was nearly 10% higher than the proportion of members who joined via standard messages (5.25%). **Conclusion:** Individuals recruited into the registry from evidence-based messages were more likely to enroll in a study compared to those who joined via standard messaging. This study demonstrates that the type of person recruited by evidence-based messages may be more motivated to participate in clinical studies than those recruited through standard messages.

We submitted 6 papers to journals for peer review.

Aim 2. We submitted the next R01 grant to the NIH in Cycle I. This grant is scheduled for a study section in late June 2026. The aims of the grant are to (1) test EHRs as a dissemination method for recruitment messages for registries; (2) develop and test new theory-based messages to encourage enrolling directly into ADRD clinical studies; and (3) test the effectiveness of each dissemination method (registry, EHR) and message type at generating interest in participating in clinical studies among adults at high risk for ADRD. Prior to the grant submission, we conducted a feasibility study with the same evidence-based message described above to test whether EHRs could be a recruitment method for registries and, ultimately, clinical studies. Evidence-based messages were sent to adults who had an "activated" PennChart (EHR) account residing in zip codes in reasonable proximity to the Penn ADRC Memory Center (Philadelphia, Montgomery, and Delaware counties), had no diagnoses of cognitive impairment. The messages asked people to join the Penn ADRC Memory Center Brain Health Research Registry (BHRR). 693 messages sent and 72 participants enrolled, with an overall enrollment rate of 10.4%. Men enrolled at a rate of 10.8%, Black at 6.9%, and Hispanic at 8.3%. **Conclusion:** The evidence-based messages developed for social media were efficient and effective at enrolling high-risk adults into a registry via an EHR, with early data suggesting EHRs are more effective than social media. This application proposes scaling up recruitment for registries (APR, BHRR) and to develop evidence-based messages for direct enrollment into clinical studies that can be disseminated through EHRs.

Aim 3. Our email newsletters are well-received, with an average open rate of 35%, and unique click rate of 10% in the past 12 months, compared to the industry standard of 16% and 1.6%, respectively. Over the past 12 months, study opportunity emails had an average open rate of 35.3% (with AZ led studies slightly higher at 36.6%) and an average unique click rate of 6.8% (with AZ led studies at 5.8%).

Aim 4. 18 Arizona ADRC / AAC researchers have submitted requests for low to no-cost assistance with their participant recruitment needs for their Arizona-based studies. An additional 7 annual renewal requests have been submitted. We are submitting an abstract to the AAC 2026 Scientific Conference describing the Registry & GeneMatch and recruitment assistance metrics to help raise awareness about our services to Arizona-based researchers.

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ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Returning Results to Research Participants. Jessica B Langbaum, PhD, Claire Erickson, PhD, Alireza Atri, MD, PhD, Matthew Grilli PhD, Matthew Huentelman, PhD, Eric M. Reiman, MD , Bryan K. Woodruff, MD. Banner Alzheimer's Institute; Banner Sun Health Research Institute; Arizona State University; University of Arizona; Translational Genomics Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

1) Aim 1: To expand the pilot test of returning clinical/cognitive and MRI results to participants in the Arizona ADRC Clinical Core from 1 Clinical Core site to other Clinical Core sites and potentially its affiliated studies (e.g., Arizona APOE Allelic Dose Study, Brain and Body Donation Program), monitor feedback from participants, and refine the program to roll out to all ADRC Clinical Core sites by end of the funding period.
2) Aim 2: To develop, test, and refine materials focused on returning genetic and biomarker results (e.g., blood test results, CSF test results, amyloid PET scans) results to participants in the Arizona ADRC Clinical Core (at least 1 Clinical Core site) and/or its affiliated studies (e.g., Arizona APOE Allelic Dose Study), monitor feedback from participants, and potentially refine the program to roll out to other ADRC Clinical Core sites and affiliated studies by end of the funding period.
3) Aim 3: To partner with other ADRCs to develop plans for return of results to all Arizona ADRC Clinical Core participants to include in our renewal application being submitted to NIH in 2025.

Background and Significance:

Research studies in AD and related dementias (ADRD) do not routinely return individual genetic, biomarker, or cognitive test results acquired during the study.[1] Numerous groups have written position statements supporting the return of individual research results and secondary findings (i.e., results that were not the primary objective of the research) under specific conditions, including when the results are clinically actionable, valid, and reliable.[2] Understandably, there is interest in understanding whether returning genetic or AD biomarker results to participants results in short or long-term emotional or psychological harm. Thus far, studies have not found psychological, emotional, or subjective cognitive harm to be caused by returning results to participants who are screened for psychological readiness to receive results.[3-6] Notably, these studies are in people who opt-in to receiving results and are screened for psychological readiness and as a result, the findings may be different in individuals pursuing direct-to-consumer testing.[7,8] The availability of amyloid modifying therapies is dramatically increasing the need for disclosure of AD related genetic and biomarker test results. In addition, the 21st Century Cares Act requires the immediate return of most medical test results, including AD biomarkers. Given the existing shortage of genetic counselors and dementia specialists, there is great need for the development and deployment of scalable self-directed methods to responsibly communicate gene and biomarker test information and results. Perhaps related to the 21st Century Cures Act and recognition that AD biomarker testing may soon be readily available,[8,9] workgroups have proposed a draft Participant Bill of Rights for ADRD studies, advocating that clinical studies are proactively designed to provide the option for participants to learn their individual research results if they choose, and in a manger that ensures study integrity.[1] Similarly, the recent Notice of Funding Opportunity for the Alzheimer's Disease Research Centers (ADRCs) (RFA-AG-24-001) requires Clinical Cores to develop and implement protocols for returning results to participants, but does not dictate which results are returned, nor the specific manner in which they are returned. The Alzheimer's Prevention Initiative (API) program has developed processes and materials for

healthcare providers to return select genetic and biomarker results to clinical trials.[10] There is considerable opportunity to adapt these processes for more scalable delivery models that may also include disclosure of cognitive test results, and well as for use in observational studies which may need to return results to participants.[2]

Preliminary Data, Experimental Design and Methods:

To acheive Aim 1, we will review data from the initial pilot phase of returning cognitive/clinical and MRI results to participants in the Arizona ADRC Clinical Core – Banner Sun Health Research Institute location, to refine the program to roll out to other Arizona ADRC Clnical Core sites and potentially affiliated studies (e.g., Arizona APOE Allelic Dose Study, Brain and Body Donation Program).

To achieve Aim 2, we will refine and adapt API Generation and eSMARTER materials for use in the Arizona ADRC and affiliated studies to return genetic and biomarker results (e.g., blood test results, CSF test results, amyloid PET scan results) to participants. The goal is to pilot test this at 1 Clinical Core site, monitor feedback from participants, and refine the program to roll out to other ADRC Clinical Core sites and affiliated studies by end of the funding period.

To achieve Aim 3, we will partner with leaders from other ADRCs (e.g., University of Pennsylvania, University of Wisconsin, University of California Irvine) to learn how other centers are planning to return results to their participants and incorporate this information in our renewal application due to the NIH in 2025.

Proposed One-Year and Long-Term Outcomes:

Results from this effort will help to inform plans for return of results to participants in the Arizona ADRC and its affiliated studies in preparation for the Center's renewal grant application in September 2025. We anticipate that the results from the pilot study will be used as preliminary data to include in our application, will be presented at scientific conferences, and may be submitted for publication in peer-reviewed journals. We may seek additional external, non-state funding from NIH, industry and/or philanthropic organizations to support our efforts to develop scalable risk-disclosure platforms and related return of results materials.

Year End Progress Summary:

Aim 1. During the funding period we revised letters for returning clinical / cognitive research diagnosis and MRI results, modifying this from a manual process to one in which the letters can be generated in an automated manner. As part of this effort, we created 2 educational worksheets to be included with disclosure letters to increase understanding of information included in the disclosure letters. One educational worksheet describes "Memory and Thinking on a Spectrum" and provides definitions for common research diagnoses (unimpaired cognition, subjective cognitive decline, impaired not MCI, mild behavioral impairment, mild cognitive impairment, dementia) and possible causes or contributors (Alzheimer's disease, Lewy Body Disease, vascular problems, frontotemporal disorders, mood, medical comorbidities, and medications). A second worksheet was designed to explain common incidental MRI findings – white matter disease and/or chronic microvascular change. We also developed a survey to gather feedback from participants about the written materials. The revised letters, educational materials and surveys were IRB approved in May 2026. The automated process to generate the disclosure letters was updated to reflect new materials. The revised materials and survey will be rolled out to additional Arizona ADRC Clinical Core sites by June 30, 2026.

During the funding period, we mailed 102 disclosure letters returning cognitive / clinical results (approximately 50% of the active ADRC clinical cohort at Banner Sun Health Research Institute (BSHRI) and 70 MRI results (34% of actively enrolled Arizona ADRC Clinical Core participants at BSHRI). To date, we have not received any questions or queries from participants or PCPs

regarding information provided in the disclosure letters. To assess understanding of disclosed results, psychological impact of receiving results, and whether receipt of the information was helpful, two surveys were developed; one survey is specific to MRI results and the other to clinical / cognitive research diagnosis.

Aim 2. We analyzed data from the API Generation Program APOE disclosure program which disclosed *APOE* genotype results to 9496 participants (including 790 *APOE4* homozygotes, 4869 heterozygotes, and 3837 non-carriers). The results were published in *Lancet Healthy Longevity* in November 2025.[11] In cognitively unimpaired, psychologically pre-screened adults, *APOE* disclosure by a trained health-care provider was generally safe and well tolerated, consistent with results from previous studies. To our knowledge, this is the largest study examining *APOE* disclosure to date, especially for homozygotes, and is notable for the older age of participants compared with previous research. These results are timely and important given anticipated increases in *APOE* disclosure to guide clinical decision making once an Alzheimer's disease prevention treatment is approved for cognitively unimpaired adults or if patients' family members are interested in genetic testing. Scalable approaches for returning Alzheimer's disease risk information are critical to meeting anticipated demand. Results from this study may be useful to bolster clinical translatability of disclosure programs. Data from the CONNECT4 APOE program (NCT02978729) were analyzed and the manuscript describing the findings was accepted for publication in *Alzheimer's & Dementia* in May 2026. The CONNECT4 data suggest both telephone and videoconference are reasonable options for disclosure of *APOE* genotype in cognitively unimpaired individuals. Videoconference disclosure may have some benefits for certain demographic groups. We published the eSMARTER trial design manuscript in *Alzheimer's & Dementia: Translational Research & Clinical Interventions* in November 2025.[12] Analyses of the eSMARTER trial data are ongoing. Topline results will be presented at AAIC in July 2026; a manuscript describing the topline findings is being prepared for submission to *JAMA Neurology* in July 2026. We will be using the CLARiTI study amyloid PET materials for use in the Arizona ADRC, though we have developed new amyloid PET materials for use in affiliated studies, such as the Arizona APOE 2.0 cohort study. These new materials were developed to return amyloid PET Centiloid values (CL), a continuous measure, rather than the binary "elevated" or "not elevated" result. As part of this effort, we intend to gather participant feedback on the materials before implementing them in a study and will measure participant feedback after their use.

Aim 3. We have continued to engage with other ADRCs. Dr. Langbaum participants in monthly meetings with Directors from all the other ADRCs and in the CLARiTI "return of results" meetings. Based on discussions with other Centers, we determined that using the CLARiTI return of PET results materials was best for the Arizona ADRC to ensure participant consistency. We submitted our renewal ADRC grant in September 2025; it was reviewed in April 2026 and received an impact score of 27. Notice of grant award (funding) is expected before the end of the federal fiscal year in September 2026.

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ARIZONA ALZHEIMER'S CONSORTIUM
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Statistical and Neuroimaging Data Science Core Resources Serving Consortium Members.
Michael Malek-Ahmadi, PhD, Yi Su, PhD, Hillary Protas, PhD, Yinghua Chen, MS, Ji Luo, MS, Wendy Lee, MS, Valentina Ghisays, PhD, Gene Alexander, PhD, Blake Langlais, MS, Ben Readhead, PhD, Ignazio Piras, PhD, Kewei Chen, PhD, Eric M. Reiman, MD. Banner Alzheimer's Institute; Arizona State University; University of Arizona; Mayo Clinic; Arizona Alzheimer's Consortium; Translational Genomics Research Institute.

Specific Aims:

1) Standardize, organize and share research data including imaging and biomarker measurements using state-of-the-art methodologies across multiple large datasets that integrate clinical, cognitive, imaging, and biomarker data.
2) Offer comprehensive statistical and image analysis consultation and collaboration as well as training services to investigators and students inside and outside Arizona based on the common interest and their needs.
3) Serve as mentors to students and early-career investigators in order to help build the pipeline of AD investigators that will be needed in the coming years.

Background and Significance:

Over the years, the CIAL team has continued to serve as a core resource for imaging and statistical expertise to facilitate AD research and collaboration, with the Arizona Alzheimer's Consortium providing much-needed funding for our analytical team, supplementing the NIH-funded ADRC Data Management and Statistics Core (DMSC). Our lab helped collaborating investigators perform imaging and statistical analysis using state-of-the-art methodologies developed by our lab and elsewhere. Additionally, various educational training activities partially supported by the State have had great impacts for our young scientists and our colleague and students. The important research and analyses performed through this grant have had lasting impact on the AD field and have generated numerous publications that otherwise would have been impossible. With this support, the lab has also helped collaborating investigators with preliminary data analysis, study design, and statistical power analysis to facilitate their grant applications and participate as part of their research team.

Experimental Design and Methods:

Aim 1. We will continue our efforts to facilitate the standardization, harmonization, organization, and sharing of imaging, biomarker, demographic, cognitive, and clinical data from the Arizona APOE cohort, Arizona ADRC, API-ADAD, ADNI, NACC, A4 Clinical Trial, and other cohorts to Consortium investigators. Working in conjunction with the DMSC of Arizona ADRC, we will develop and implement procedures that facilitate and track data sharing and utilization.

Aim 2. We will continue our effort in working and supporting ADRC DMSC to provide data access, data analysis services, and participating in collaborative studies.

Proposed One-Year and Long-Term Outcomes:

In the upcoming year, we will continue organizing and curating imaging-derived measures and integrate them into our database for our local cohorts and large open-science databases and make them available to collaborators. In addition to the imaging data we are continuing to receive blood biomarker data from Dr. Nick Ashton's lab for several different cohorts and are integrating these data with the existing neuroimaging data. We will continue to work closely with and support the ADRC DMSC to provide imaging and especially statistical services to ADRC investigators,

and those inside and outside Arizona Alzheimer's Consortium. We anticipate high-quality publications and grant submissions as part of the collaborative effort. In the long term, we anticipate being able to help grow the research portfolio of Consortium investigators through our methodology development, statistical service, and assistance.

Year End Progress Summary:

Aim 1 Progress:

During the current funding period, we substantially expanded and harmonized our multimodal Alzheimer's disease research data repository to support the development and validation of advanced machine learning models. The curated resource now includes data from 11 major national and international cohorts, comprising more than 45,000 structural MRI scans, 16,800 amyloid PET scans, and 7,100 tau PET scans from over 22,000 participants. These datasets encompass a broad spectrum of cognitively normal individuals, participants at risk for Alzheimer's disease, and individuals with mild cognitive impairment and dementia, and include associated demographic, clinical, cognitive, imaging, and blood-based biomarker data. Key cohorts include ADNI, NACC/SCAN, A4, HABS-HD, OASIS3, WRAP, the Arizona APOE and Arizona ADRC cohorts, and the API Generation studies. To ensure data consistency and facilitate cross-cohort analyses, all imaging data continue to be processed using standardized and validated MRI and PET analysis pipelines developed and maintained by our group. We have further implemented harmonization strategies to address differences across imaging platforms and study protocols, including standardized preprocessing, image- and feature-level harmonization, and AI-based methods for reducing site- and scanner-related variability. We will continue to incorporate new data releases and additional cohorts in the upcoming year to enhance its scientific value.

Aim 2 Progress:

In the past year, led by Dr. Malek-Ahmadi's collaboration with Dr. Sydney Schaefer at ASU, our team continued to support the joint effort to examine motor function changes in aging and AD. Analysis using the Roche Elecsys ptau-217 and Abeta-42 assays were recently completed for over 400 subjects from the Longevity Study and have been made available to Dr. Schaefer. In addition, Drs. Malek-Ahmadi and Su are listed as co-investigators on two different R01 applications that Dr. Schaefer submitted during this funding cycle. Dr. Malek-Ahmadi has also submitted an abstract to the 2026 Arizona Alzheimer's Consortium Conference using this new Roche ptau-217 and Abeta-42. Dr. Malek-Ahmadi was also selected to give an oral presentation at the 2026 Alzheimer's Association International Conference that will be held in London. This presentation will be on work he did using newly-acquired ptau-217 data from the Arizona APOE Cohort to determine the classification accuracy of amyloid-positive status across all 6 APOE genotypes. This abstract has also been submitted for presentation at the 2026 Arizona Alzheimer's Consortium Conference.

Outside of the Consortium, our team continued to work with Dr. Quiroz (MGH) to examine biomarker changes in relation to APOE genotypes and inherited forms of AD and sex differences as well as with Dr. Suchy-Dicey, leveraging the data from the Native American cohort from the Strongheart study, we are currently examining how diabetes and chronic kidney disease affect brain structure and cognitive function with a manuscript in preparation.

Aim 3 Progress:

We continue to serve as a resource for students at institutions across Arizona to participate in research within our ongoing portfolio of activities and collaborations. Dr. Malek-Ahmadi continues to serve as a Co-Director of the Banner-ASU Neuroscience Scholars program where, in addition to his administrative role, he works with 2-4 students each summer who undertake various research projects using the datasets described in Aim 1 Progress. Dr. Malek-Ahmadi also mentors

students who come into contact with him via the University of Arizona College of Science Job Shadow Program as well as through the UA-COM Phoenix.

A list of projects and investigators supported by this award during this funding year included:

a. Dr. Quiroz (MGH), supporting collaboration with her on the investigation of AD risk factors in autosomal dominant AD populations. (Malotaux et al. J Prev Alz. Dis. 2026 PMC13157058; Tristao-Pereira et al. Brain Commun. 2026 PMC12816921; He et al. Alz. & Dem. 2026 PMC12756048; Malotaux et al. Alz. & Dem. 2025 PMC12208796)
b. Dr. Suchy-Dicey (Huntington Medical Research Institute), supporting collaboration with her research of AD and aging in Native American population. (two manuscripts under development)
c. Dr. Sydney Schaefer (ASU), supporting her development of novel motor tasks in the application of AD related research and her grant application.
d. Dr. Thomas Beach (BSHRI), providing statistical support to his research.
e. Dr. Alireza Atri (BSHRI), providing statistical support to his research.
f. Dr. Yalin Wang (ASU), continuing support our collaboration with him on the application and investigation of ML/AI techniques in AD/ADRD research and support his grant application efforts. (Chen et al. IPMI 2026 PMC12965764)
g. Dr. Fang Yu (ASU), continued collaboration and imaging/data analysis support to her non-pharmaceutical intervention studies. (Yu et al. Trials 2025 PMC12522579)
h. Dr. Smith (John Hopkins), providing our multi-modal imaging data analysis for her late-life depression study including new MCI and longitudinal data. (supported two R01 applications)
i. Dr. Steven Rapcsak, (BAI-Tucson), supporting his analysis of blood biomarker and MRI data.
j. Dr. Ryan et al. (UofA), supporting the UofA Brain and Body Imaging Center
k. Dr. Alexander (UofA), supporting Network Imaging and Lifestyle Biomarkers for Evaluating Vascular Contribution to Brain Aging and AD.
l. Dr. Madappa Kundranda, (Banner MD Anderson Cancer Center), providing sample size estimation for a clinical trial
m. Neelima Maripudi, (Banner Children's Hospital), statistical support for NICU data.
n. Dr. Maxwell Leung, (ASU), supporting his analysis of the behavioral effects of cannabis use in dogs.

With this funding support, in conjunction with the NIH-funded Arizona ADRC DMSC, our team facilitated the Pilot Research Projects and Developmental Projects program sponsored by ADRC and Consortium funding. We also supported 17 additional grant applications and 14 publications. We anticipate continuing this effort to support Consortium and external investigators in the upcoming year.

Select Publications:

Malek-Ahmadi M, Reed AM, Guan DX. Most Neuroscience Data Is Not Normally Distributed: Analyzing Your Data in a Non-normal World. eNeuro. 2026;13(1):ENEURO.0414-25.2025.

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ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Health Equity Outreach, Recruitment, and Retention Program. Lori Nisson, LCSW, Jessica B. Langbaum, PhD, Po-Heng Tsai, MD, Alireza Atri, MD, PhD, Eric M. Reiman, MD, Nicole Lomay, Heather Mulder, David Parkhurst, and David Coon, PhD. Banner Alzheimer's Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium; Arizona State University; Banner Alzheimer's Institute - Tucson.

Specific Aims:

1) To forge and maintain working relationships with members of our high-risk communities in the awareness, care, and scientific understanding of Alzheimer's disease (AD) and related disorders, through educational and service-related community-based activities.
2) To support the Arizona Alzheimer's disease Research Advisory Committee's work to help establish policies related to Indigenous Data Sovereignty for our ADRC and affiliated studies open to all.
3) To create novel opportunities to reach under-represented community members through consistent education and support programs and sharing current information about study opportunities, including enrolling in a research registry.

Background and Significance:

Many Americans face the problem of Alzheimer's disease (AD) there are a large number of high-risk communities in Arizona. Since 2006, we have established an outreach program to help address the educational and clinical needs of all patients, families, and health care professionals; developed socially relevant educational and service programs; and demonstrated to underserved communities our strong interest in serving their needs, whether or not they choose to participate in research studies. In 2022, we paused our efforts to recruit new participants, including pausing our partnership with Medstar's Strong Heart Study site in Phoenix, while we formed an Alzheimer's disease Research Advisory Committee for our ADRC and affiliated programs. The Committee has been tasked with working to be inclusive of all communities to create a data sharing plan, after which we could re-open research enrollment to underrepresented communities and individuals interested in participating in the Clinical Core or other studies to ensure innovative approaches for access and optimal continuity of care, quality of care, especially for underserved populations.

Preliminary Data, Experimental Design and Methods:

More than 108 high risk Americans have been enrolled into the Arizona Alzheimer's Disease Research Center (ADRC) Clinical Core across the consortium as of June 2026; of those, 107 have their data uploaded to the National Alzheimer's Coordinating Center (NACC) database, the majority from the BAI-Phoenix study site. There are 60 actively enrolled Native Americans in the ADRC Clinical Core at Banner Alzheimer's Institute-Phoenix. Both the pandemic with Covid-19 restrictions during the Public Health Emergency up until May 2023, and a pause in recruitment in late 2022, placed limitations on our recruitment goal of enrolling 75 participants including underserved members in our clinical core. In October 2023, we resumed recruitment of new Native American participants, once we were able to put policies in place to ensure Data Sovereignty, by establishing earlier in 2023 an Alzheimer's disease Research Advisory Committee. The committee is tasked with working with leaders and stakeholders to create Data Sovereignty and data sharing plan, to include the review and potential approval of future research studies. Formation and outline of responsibilities of the committee allowed the BAI Phoenix site to renew its partnership with Medstar's Strong Heart Study locally.

We anticipate that resuming increased health equity focused recruitment in concert with participant education about Alzheimer's and related disorders will offer an opportunity to acquire needed imaging and blood biomarkers in cognitively healthy as well as cognitively impaired high-risk Americans. Development of a biologically and ultimately medically meaningful preliminary dataset for future studies relies on increasing the number of participants opting to undergo these tests, in turn expanding the dataset to become a robust way to gain scientific knowledge about this underrepresented population.

As tribal communities continue to recover from pandemic conditions, presentations and outreach activities have been growing in tribal communities over the past few years. In some communities' Covid-19 restrictions prevailed through 2023, and there remain many limitations in staffing within these programs that seek to provide education and support services to elders and family caregivers. Many tribes have been working to sustain their communities' needs, manage complex and challenging circumstances and remain connected with limited internet access. Given these circumstances, the outreach team has continued to be nimble to accommodate opportunities to collaborate with departments serving adult and senior adult populations.

In October 2025, the outreach team held the 19th Annual Alzheimer's Disease and Dementia in Native Americans conference at Little America Hotel in Flagstaff, Arizona. Sixty-seven professionals working in tribal communities attended the pre-conference, and 172 other professionals, elders, and caregivers attended the full-day conference. The conference reached 15 unique tribes with representation from across Arizona, California, and New Mexico. Topics guided by our Native American conference advisory council included an Alzheimer's Overview and Research Update, Culturally Relevant Small Steps for Big Impact and Putting it Into Practice, Dementia Untangled: Caregiver Experience, Communication Tips to Connect Through Disease Progression, and Caregiver Self-Care. There was a high level of satisfaction voiced verbally and revealed through post-program evaluations.

Our Native American Outreach continues to expand our reach by providing Native American Beacon Newsletters with quarterly deliveries to 4,000 tribal caregivers and persons with memory loss through meal pick-up and delivery programs, ensuring they receive critical caregiving education and strategies. In addition, our outreach team provided more than twelve timely topics within our Circle Group for caregivers, including brain health, dementia caregiver education, care strategies, and ADRD information to Arizona tribal communities and tribal communities nationally. Our team trained 1,557 formal caregivers and other professional workers on a variety of topics such as Alzheimer's Fact or Fiction, Overview of Alzheimer's Disease, Balance for Brain Health, and Dementia Friends informational sessions. In addition, the team presented the BAI "Walk with Me" tribal music CD and the Native American Toolkit Refresher to train professionals serving tribal communities. The team also made connections with tribal families living with dementia to provide our comprehensive culturally relevant Navigating Memory Loss guides, Walk with Me CD, and Caregiver TIPS cards.

The American Indian/Native American Alzheimer's Disease Research Advisory Committee is currently co-chaired by Cynthia West, Wyandotte Nation, and Ginger Sunbird Martin, Gila River Indian Community. The other Committee members include Grandmother Pershlie "Perci" Ami, Dr. Megan Christopher, Violet Mitchell-Enos, Bethany Reed, John Molina, and Jennifer Thompson. The Committee is charged with providing guidance on establishing partnerships with Tribal communities in Arizona and on a range of issues related to Indigenous Data Sovereignty, including the extent of research involvement of high-risk individuals who identify as American Indian/Native American but may not reside on Tribal land; how data and biological sample collection is shared with tribal communities; and how and when researchers may be allowed to

use this data for scientific purposes. Their efforts may complement similar efforts at the national level. In 2025/26, we continued our work with the American Indian/Native American Alzheimer's Disease Research Advisory Committee and developed materials to reach out to each tribal community and met with the executive director of the Inter-Tribal Council of Arizona to request time on Tribal Leaders meeting upcoming agenda to seek advice on approaching tribal leaders about Alzheimer's-related research opportunities that may be of interest to members of their community who may choose to participate.

Proposed One-Year and Long-Term Outcomes:

1. Continue outreach efforts to high-risk communities and education of at least 50 professional care providers serving underserved communities to increase health equity related to diagnosis and treatment of Alzheimer's and related disorders through our annual preconference intensive, toolkit trainings and opportunities to participate in quarterly BAI Project ECHO professional tele-mentoring program.
2. Support the Arizona Alzheimer's disease Research Advisory Committee's efforts to meet quarterly to develop policies related to Data Sovereignty, research involvement of individuals who identify as American Indian / Native American (but may not reside on Tribal lands), data and biological sample collection, and sharing of data and samples with Tribes and other researchers.
3. Elevate opportunities to reach and engage more high-risk community members from youth to elders to raise community awareness of brain health and dementia care.
    a. Provide at least twelve education programs reaching 750 elders, care partners, professionals, and community members.
    b. Offer at least ten timely topics within our Circle Group on brain health, dementia education, caregiver strategies, and study opportunities.
    c. Offer quarterly digital specialty BAI Beacon newsletters reaching 4000 family caregivers and community members with topics on caregiving, support programs and care and research options.
    d. Increase national engagement, knowledge, and collaboration amongst clinicians and researchers treating underrepresented communities and all others using data gathered through the study. Leverage available data for educational purposes at the annual Conference on Alzheimer's disease and dementia to optimize health promotion and elevate research opportunities and the Arizona Alzheimer's Prevention Registry among medically underserved and low-resource populations reaching a minimum of 180 participants.

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Expanding Biomarker Discovery for Dementia in SPRINT. Jeremy Pruzin, MD. Banner Alzheimer's Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

1) Identify additional potential plasma biomarkers using the NULISA central nervous system (CNS) protein panel that may add to established Alzheimer's disease (**AD**) and AD-related dementia (**AD/ADRD**) biomarkers in explaining the emergence of MCI/dementia as an ancillary study of a larger, more comprehensive project obtaining established AD/ADRD biomarkers and APOE *ε4* genotypes from stored samples from the Systolic Pressure Intervention Trial (**SPRINT**).[1]
2) Create a public data repository integrating novel central nervous system (CNS) panels protein assays and APOE *ε4* data with existing clinical, MRI, neuropsychological, and MCI/dementia outcome data from SPRINT.

Background and Significance:

Alzheimer's disease (**AD**) and AD-related dementias (**AD/ADRD**) are leading causes of dependence, disability, and death in older adults, projected to affect 153 million people globally by 2050. Hypertension (**HTN**) occurs in 50% of US adults by age 50 and 75% by age 65, increasing the risk of both AD dementia and Vascular Cognitive Impairment and Dementia (**VCID**), which together account for ~90% of all dementia diagnoses. Black and Hispanic adults in the US have higher average blood pressure (**BP**) and lower rates of BP control compared to other racial and ethnic groups, contributing to a 1.5 to 2 times higher incidence of AD/ADRD compared to White adults despite both groups having less brain beta-amyloid (**Aβ**). SPRINT, which included 9,361 US adults from heterogenous racial/ethnic backgrounds, found that intensive vs standard systolic BP (**SBP)** treatment (<120 vs <140 mm Hg) significantly reduced the risk of emergent mild cognitive impairment (**MCI**) or dementia. Epidemiological evidence suggests a likely synergism between SBP and AD pathology, but significant gaps remain in our understanding of the role AD pathology plays in how intensive SBP control affects MCI/dementia risk overall and if there are differences by sex, age, race/ethnicity, and *APOE ε4* (***ε4)*** genotype. Understanding how intensive SBP control affects dementia risk in the presence or absence of AD pathology and by sex, age, race/ethnicity, and *ε4* can refine HTN treatment strategies to lower dementia risk, inform future trial designs, and promote more equal health outcomes between different populations.

For the larger project, we will assess AD/ADRD plasma biomarkers in longitudinal (4 time points; median 7 years follow-up; n=8,797, mean age at baseline 68 years, 40% Black or Hispanic participants) stored SPRINT blood samples. Using this data, we will determine (1) Whether baseline AD pathology or *ε4* modify effects of intensive SBP control on MCI/dementia; (2) Whether intensive SBP control reduces longitudinal change in AD biomarkers (ptau217, Aβ 42/40) or neurodegeneration (neurofilament light; NfL), and how this varies by baseline AD pathology presence, *ε4*, race/ethnicity, age and sex; (3) Whether measures of vascular remodeling (placental growth factor; PlGF) and neuroinflammation (glial fibrillary acidic protein; GFAP) decrease with intensive SBP control. For this ancillary exploratory project, we will investigate novel biomarker candidates assessed on the NULISA platform from the CNS panel at baseline only that may add in predicting dementia risk.

Overview of SPRINT and evidence that SBP control reduces MCI and dementia incidence. SPRINT was a multicenter, RCT comparing two SBP treatment goals—intensive control (<120 mm Hg) versus standard control (<140 mm Hg) —in those at high cardiovascular disease (**CVD**)

risk, excluding those with diabetes, prior stroke, or dementia at baseline.[7,9] The primary results showed that intensive SBP control reduced CVD events by 25% (hazard ratio [HR] 0.75; 95% CI, 0.64–0.89) and all-cause mortality by 27% (HR 0.73; 95% CI, 0.60–0.90) over a median follow-up of 3.26 years.[2] SPRINT MIND was an integral part of SPRINT, investigating the effects of intensive vs standard SBP control on adjudicated all-cause dementia and MCI. Clinical assessments continued for a median of 5.1 years, with 8,563 participants (91.5%) completing at least one follow-up assessment. All MCI and dementia cases were adjudicated by an expert committee blinded to treatment assignments (**Figure 1**).[3] Although the direction of the effect suggested benefit, intensive SBP control did not significantly reduce the incidence of dementia alone, it did however significantly reduce the risk of MCI and the combined incidence of MCI or dementia (**Table 1**). Supporting evidence for the benefits of intensive BP control on dementia comes from a meta-analysis of 12 RCTs involving 92,135 participants, including SPRINT, which found that lowering BP with anti-HTN medication reduced the risk of AD/ADRD (odds ratio 0.93; 95% CI, 0.88–0.98) over four years.[4] This level of risk reduction could translate into a very meaningful public health impact given the extremely high prevalence of HTN in the US population and globally. Additional support for the benefits of BP control comes from the China Rural Hypertension Control Project, an RCT that demonstrated more intensive BP control resulted in reduced dementia incidence over four years with an effect size similar to what was found in SPRINT (HR 0.85; 95% CI, 0.76–0.95).[5] SPRINT MIND 2.0 extended the follow-up of participants beyond the original trial, resulting in a median follow-up period of 7 years and capturing 306 additional MCI and dementia events. SPRINT MIND 2.0 demonstrated that that intensive SBP control during the 3.3 year intervention period was associated with reduced incidence of MCI/dementia even though group SBP differences were no longer maintained after the trial's conclusion (HR 0.89; 95%CI, 0.79–1.00), suggesting that intensive SBP control exerts durable benefits on MCI/dementia beyond the intervention period.[6]

Preliminary Data, Experimental Design and Methods:

In this exploratory, hypothesis-generating aim, we will leverage ultra-high sensitivity assays to examine a broader range of plasma biomarkers using the NULISA platform. Our goal is to identify novel biomarkers that predict MCI/dementia across diverse subgroups. We will use 871 MCI/dementia cases captured during the SPRINT planned follow-up period and 871 matched controls, with a focus on detecting unique biomarker profiles that may improve risk prediction for MCI/dementia emergence, especially for those that are AD pathology negative (AD-) at baseline. Sample selection will include all adjudicated MCI/dementia cases during the initial SPRINT follow-up period. To ensure comparability between cases and controls, we will use 1:1 deterministic matching on key covariates: age (±2 years), sex, race/ethnicity (e.g., White, Black, Hispanic, Other), *ε4*, treatment arm, and history of CVD to the extent possible, ensuring a well-matched control for each case. Samples will be obtained from the BioLINCC repository at the National Heart Lung and Blood Institute.

Proposed One-Year and Long-Term Outcomes:

One Year Outcomes

- **Completion of NULISA CNS panel assays** on 1,742 baseline SPRINT plasma samples (871 MCI/dementia cases and 871 matched controls).
- **Preprocessing and integration** of NULISA protein data with APOE genotype, clinical, neuropsychological, and adjudicated MCI/dementia outcome data.
- **Principal component and multivariable modeling analyses** to identify biomarker clusters and novel signatures associated with MCI/dementia risk.

- **Submission of one abstract** to a national scientific meeting (e.g., AAIC, Society for Neuroscience, or CTAD) highlighting preliminary findings from novel biomarker analyses.

Long Term Outcomes

- **Identify novel plasma protein biomarkers from the NULISA CNS panel** that improve prediction of MCI/dementia beyond established AD biomarkers.
- **Characterize biomarker profiles associated with dementia risk** that reflect vascular dysfunction, synaptic loss, or neurodegeneration, using NULISA's broader protein coverage.
- **Determine whether distinct NULISA biomarker patterns are enriched in specific subgroups**, such as APOE ε4 non-carriers, AD biomarker-negative individuals, or those from underrepresented racial/ethnic groups.
- **Establish the added value of multi-protein NULISA signatures** for stratifying dementia risk across diverse populations.
- **Facilitate future hypothesis-driven studies** by identifying specific NULISA proteins or clusters that warrant mechanistic investigation.

Year End Progress Summary:

APOE genotyping has been completed, and these data are available for integration with the planned NULISA protein measures and existing SPRINT clinical and outcome data. Plasma samples have been transferred from the University of Utah to Banner Sun Health Research Institute (BSHRI), where the NULISA CNS panel assays will be performed in the laboratory of Dr. Nicholas Ashton. The assays are prepared and slated to run but have not yet been performed. Because the NULISA measurements are pending, the planned preprocessing and integration of the protein data and the principal component and multivariable modeling analyses have not yet begun; these will proceed once the assays are complete.

The one-year deliverable of submitting an abstract to a national scientific meeting has been met. An abstract reporting the APOE-related findings described below was submitted to the Clinical Trials on Alzheimer's Disease (CTAD) conference.

Findings

Using the completed APOE genotype data, preliminary analyses indicate that intensive systolic blood pressure control was modestly more effective in APOE ε4 carriers than in non-carriers. This result is being prepared as a manuscript for submission to JAMA Neurology. The finding speaks directly to the project's interest in whether treatment effects and biomarker signatures differ across genetically defined subgroups, and it provides an early foundation for the subgroup analyses planned once NULISA data are available.

Challenges

The principal challenge during this period was logistical rather than scientific. Transfer of the shared SPRINT plasma from the University of Utah to BSHRI was staged deliberately so that the specimens could be coordinated and organized appropriately before assay, which added time on the front end. In addition, because the plasma is a limited, shared resource used by both this ancillary project and the larger parent SPRINT biomarker project, the team is being strategic about how the available volume is allocated across studies to preserve sample integrity and avoid unnecessary use. The NULISA assays are expected to run within the next several months, after which preprocessing, integration, and analysis will proceed as proposed.

Progress Toward Proposed Long-Term Outcomes:

The long-term aims depend on completion of the NULISA assays, and the groundwork for them is now in place: specimens are staged at BSHRI, APOE genotypes are available for integration, and the analytic plan is defined. The preliminary APOE finding advances the long-term goal of determining whether biomarker and treatment-response patterns are enriched in specific subgroups, such as ε4 carriers and non-carriers. Once the CNS panel is run, the project will pursue identification of novel plasma biomarkers that add to established AD markers, characterization of profiles reflecting vascular dysfunction, synaptic loss, and neurodegeneration, and evaluation of the added value of multi-protein signatures for stratifying dementia risk across diverse populations.

Publications, Presentations, Collaborations, and Future Applications

An abstract has been submitted to CTAD, and a manuscript reporting the APOE findings is in preparation for JAMA Neurology. The project has strengthened an ongoing collaboration among Banner Alzheimer's Institute, the biomarker laboratory of Dr. Nicholas Ashton at BSHRI, and the University of Utah as the source of the SPRINT biospecimens. The work continues to align with and support the larger parent SPRINT blood biomarker effort, and the biomarker and genotype resources developed here are expected to inform future hypothesis-driven analyses and subsequent grant applications.

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Centralized Data Management Program for Arizona's Alzheimer's Disease and Related Studies. Yi Su, PhD, Jessica B. Langbaum, PhD, Eric M. Reiman, MD, Ricardo Amador, MS, Robert Bauer and colleagues from each of the participating sites. Banner Alzheimer's Institute; University of Arizona; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

1) In collaboration with the ASU team, update the AAC Tools web portal and its associated platform to support a dashboard system.
2) Continue to support the migration to UDSv4 in collaboration with NACC and integrate the UDS dataset with local data across Arizona sites and cohorts.

Background and Significance:

The Arizona Alzheimer's Consortium supports three internationally recognized longitudinal research programs that contribute significantly to the global scientific effort against Alzheimer's disease (AD), Parkinson's disease (PD), related neurodegenerative disorders, and the study of normal brain aging. These programs share common data elements, are currently managed independently, and stand to gain even greater value through a unified data management system optimized to support their shared and complementary research goals.

1. **Arizona ADRC:** Supported by the National Institute on Aging (NIA), the Arizona ADRC is the nation's first multi-site NIA-funded AD Center, with clinical sites at Mayo Clinic Arizona, Banner Sun Health Research Institute (BSHRI), University of Arizona, Barrow Neurological Institute, and Banner Alzheimer's Institute (BAI). The center annually assesses approximately 500 individuals, including those with AD, related disorders, and cognitively unimpaired older adults. Participants include APOE4 carriers and non-carriers, members of Latino and Native American communities, and other cognitively impaired and unimpaired research participants. The ADRC serves as a vital resource for collaborative research, generating new findings, publications, and grants.
2. **Brain and Body Donation Program (BBDP):** The BBDP at BSHRI includes over 800 annually assessed participants from the ADRC, the NINDS-supported National Brain and Tissue Resource for PD (NBTR-PD), and other research cohorts. With more than 1,500 completed brain donations, it provides unparalleled access to neuropathological data and high-quality brain and body tissues. The BBDP is a world-leading resource for neurodegenerative disease research and has contributed to hundreds of scientific publications and grants in AD, PD, and aging research.
3. **Arizona APOE Study:** Funded by the NIA, the State of Arizona, Mayo Clinic, and BAI, this study tracks individuals with varying APOE genotypes (ε2, ε3, ε4), representing six distinct levels of genetic risk for AD. It includes participants with rich neuroimaging and biomarker data and has played a pivotal role in advancing the concept of preclinical AD. It also laid the groundwork for the Alzheimer's Prevention Initiative (API) and the development of data-driven approaches to assess early AD changes and evaluate prevention strategies.

Together, these programs provide extensive imaging, biomarker, cognitive, and clinical data and would benefit from a coordinated data management infrastructure to further accelerate discovery, collaboration, and translational impact. Additional Consortium-led longitudinal programs may also benefit from shared infrastructure or enhanced data findability mechanisms in the future.

Preliminary Data, Experimental Design and Methods:

The data management team has continued to enhance our reporting and data infrastructure, incorporating feedback from ADRC and Consortium investigators and participating sites. We have maintained close collaboration with stakeholders to ensure access to accurate enrollment data, including records of visits that are pending finalization or have not yet been entered into NACC. This process has been supported by our adapted header information form in REDCap, which assists sites in monitoring and increasing both overall enrollment and imaging visit completion. Based on these data reports, we have also coordinated with sites to submit appropriate milestone packets for participants lost to follow-up or with minimal engagement. In parallel, we have sustained management of the Arizona ADRC cohort data, supporting both internal investigators and external collaborators. This includes ongoing curation of imaging, biomarker, cognitive, clinical, and demographic data from the Arizona APOE study, as well as from multi-site studies like ADNI and NACC. To further streamline operations and data accessibility, we have initiated the development of a comprehensive Dashboard. This tool will generate structured reports to support detailed analysis, facilitate project management, and promote data-driven decision-making across studies. Additionally, we are actively preparing for the transition to UDSv4, implementing the necessary steps to ensure a smooth migration.

With the transition to NACC's UDSv4 as the standard data collection instrument by June 2025, we will continue to update our infrastructure to ensure timely and accurate submission of UDS data to NACC. This includes modifications to our REDCap database structure and enhancements to program-level reporting tools. Timely data submission and resolution of errors and alerts remain critical to the continued success of our ADRC and related research initiatives. We will maintain our protocol of uploading imaging sessions from the Clinical Core to the SCAN, with affiliated program imaging data submitted one year post-session. Additionally, we will continue collaborating with BSHRI to prioritize the transmission of legacy UDS data to NACC, particularly for participants who have contributed imaging and/or biospecimens. Biospecimen management remains consistent, with routine shipments to the National Centralized Repository for Alzheimer's Disease (NCRAD), and ongoing reconciliation of shipment reports.

In collaboration with the ASU Biostatistics Core, led by Dr. Din Chen and David Parizek and supported by Sean Dudley, we are undertaking a major update of the Arizona Alzheimer's Consortium (AAC) Tools. This includes migrating the platform to ASU, updating the backend (which has not been refreshed in over two years), and resolving issues of compatibility and system instability. Enhancements will also include UDSv4 integration, a robust data discovery interface, and improved reporting capabilities, guided by feedback from Center and Consortium teams. This work will lay the foundation for an interactive dashboard system to better serve investigators and streamline data access and analysis.

Proposed One-Year and Long-Term Outcomes:

1. A fully functional data discovery and reporting portal that facilitates data and progress tracking in addition to research efforts
2. Ensure a successful transition to UDSv4 and continued timely and accurate data transmission to NACC and other affiliated programs

We also anticipate the establishment of a new collaborative data management team between BAI and ASU to facilitate the successful center grant renewal and long term success of the Center and Consortium

Year End Progress Summary:

With the support of David Parizek and Sean Dudley at Arizona State University, we have successfully rebuilt and modernized the Arizona ADRC dashboard system based on the previous AACTools platform. The new web-based dashboard serves as a centralized data management and reporting resource for the Arizona ADRC and affiliated programs, providing investigators and

study staff with intuitive access to participant enrollment status, UDS3 and UDS4 core data, issue tracking, and automated summary reports. To improve data management and interoperability, the system incorporates an R2R (REDCap-to-Relational) tool that converts REDCap data into a relational database, facilitating efficient data organization, quality control, querying, and long-term archiving across ADRC and affiliated projects. In addition to study data management functions, the dashboard includes curated libraries of NACC resources, Arizona ADRC-associated publications, funded grants leveraging ADRC resources, and clinical trials utilizing ADRC participants, providing a comprehensive resource for tracking Center activities and research productivity. The system has undergone internal testing and evaluation by key Center investigators, and integration with both the REDCap and NACC databases is currently underway following the recent execution of the tri-institutional data sharing agreement. During the next grant cycle of our ADRC, we anticipate transitioning the dashboard to the Arizona ADRC Data Management and Statistics Core (DMSC) for long-term maintenance, continued development, and broader deployment to support Center operations and collaborative research.

With support from the Arizona Alzheimer's Consortium (AAC), in conjunction with NIH-funded Arizona ADRC grants, our team made substantial progress in modernizing the Center's data infrastructure through the transition from the NACC Uniform Data Set version 3 (UDSv3) to the new UDS version 4 (UDSv4) standard. During the current funding cycle, we successfully managed this complex transition by maintaining parallel REDCap instances for UDSv3 and UDSv4, ensuring uninterrupted data collection while preserving the ability to perform backtracking, quality assurance, and post hoc error correction for legacy UDSv3 records. This dual-system approach has minimized disruption to ongoing studies and safeguarded the integrity and continuity of the Center's longitudinal clinical data. In parallel, our team continued to maintain and enhance the XNAT imaging informatics platform to support secure storage, organization, and sharing of neuroimaging data generated by the Arizona ADRC and affiliated research programs. We also maintained ongoing data exchange and coordination with the National Alzheimer's Coordinating Center (NACC) and other national research initiatives, ensuring timely data submission, compliance with evolving standards, and interoperability across collaborating institutions. These efforts have strengthened the Center's data infrastructure and collaborative capabilities, and we will continue to expand and support these resources during the upcoming funding year.

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Advanced Imaging Data Analysis and ML/AI in Alzheimer's Research. Yi Su, PhD, Hillary Protas, PhD, Javad Sohankar, PhD, Michael Malek-Ahmadi, PhD, Dhruman Goradia, PhD, Valentina Ghisays, PhD, Yinghua Chen, MS, Ji Luo, MS, Shan Li, MS, Wendy Lee, MS, Kewei Chen, PhD, Yalin Wang, PhD, Qi Wang, PhD, Benjamin Readhead, MBBS, Teresa Wu, PhD, Eric M. Reiman, MD. Banner Alzheimer's Institute; Arizona State University; Arizona Alzheimer's Consortium; University of Arizona; Banner Sun Health Research Institute.

Specific Aims:

1) Continued development of advanced analysis methods that facilitate high-throughput data analysis and automated quality assurance
2) Continued development of machine learning (ML) and deep learning (DL) techniques in AD and aging research.
3) Serving AAC and the broad scientific community, facilitating grant development and scientific publications through data and analytical tools sharing.

Background and Significance:

Alzheimer's disease (AD) is a devastating neurodegenerative disorder that affects millions of families worldwide and imposes a profound societal burden. Despite decades of intensive research, AD remains a complex disease, neuropathologically characterized by extracellular amyloid plaque deposition and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein, with strong contributions from genetic factors. Neuroimaging is a critical tool in the characterization and study of AD and related dementias, enabling the in vivo measurement of hallmark pathologies such as amyloid and tau accumulation. In addition, imaging also allows for the assessment of other AD-associated brain changes, including reductions in glucose metabolism, inflammatory activation of microglia, synaptic density alterations, and regional brain atrophy, all of which can be monitored longitudinally using positron emission tomography (PET) and magnetic resonance imaging (MRI). The Computational Image Analysis Laboratory (CIAL) at the Banner Alzheimer's Institute (BAI), along with our collaborators, has a longstanding track record of developing and validating advanced statistical and analytical methodologies to drive progress in AD and neuroscience research. Our contributions have significantly advanced the field's ability to detect, quantify, and understand the neurobiological changes associated with AD, we will continue this effort in the upcoming year.

The rapid growth of imaging and multi-omics datasets has created an urgent need for advanced analytical approaches capable of fully leveraging these rich resources to enhance our understanding of Alzheimer's disease (AD) and Alzheimer's disease-related dementias (ADRD), and to accelerate the development of effective treatment and prevention strategies. In recent years, there has been a marked increase in the adoption of machine learning (ML) and artificial intelligence (AI) techniques for the analysis of AD/ADRD datasets and the investigation of disease mechanisms. Our team, in collaboration with colleagues at ASU, has made substantial advances in this area, including the application of ML/AI techniques to advanced image analysis, multi-omics data integration, and the prediction of biological age. We will maintain our momentum by further advancing the investigation and application of ML/AI techniques in the upcoming project year.

The CIAL team has developed substantial expertise in imaging preprocessing and quantitative analysis, curating a comprehensive suite of imaging tools—both in-house and externally developed. In recent years, we have focused on streamlining image analysis workflows and have generated a large database of uniformly processed imaging data from studies conducted within the Consortium and in external multi-center collaborations. Building on this foundation, we plan

to expand our efforts by incorporating additional cohorts into this growing resource. We will continue to collaborate with investigators both within and outside the Consortium, offering access to our expertise, tools, and processed data to help accelerate research in AD/ADRD and the development of effective treatments.

Preliminary Data, Experimental Design and Methods:

Our team has continued to develop and maintain standardized neuroimaging analysis pipelines that are widely used by the research community. To date, we have processed over 41,000 T1-weighted MRI scans and 14,500 PET scans (amyloid, tau, and FDG) from multiple cohorts, including ADNI, NACC, AIBL, OASIS, and Arizona-based studies such as the ADRC and APOE cohorts. We will continue to expand these pipelines, process additional datasets, and work with the Data Management and Statistics Core to make imaging-derived measures broadly available to support collaborative research.

We have also advanced machine learning (ML) and deep learning (DL) approaches to characterize structural brain aging and Alzheimer's disease. Our models estimate brain age from T1-weighted MRI with an accuracy of approximately 3–4 years and have demonstrated utility in predicting MCI-to-AD progression, differentiating clinical groups, and improving prediction of amyloid positivity when combined with blood-based biomarkers. Building on these efforts, we are developing BrainPath, a generative DL framework that models individualized brain aging trajectories from a single MRI, enabling personalized longitudinal assessment of brain structural changes. We will continue expanding these ML/DL approaches to improve understanding of brain aging and AD.

In collaboration with Dr. Qi Wang at Arizona State University, we are applying deep learning to transcriptomic data to investigate molecular mechanisms underlying AD. Using multilayer perceptron models and SHAP-based interpretation, we identified brain region-specific, microglia-related, and sex-specific gene networks associated with AD progression, with findings validated in independent cohorts. We will continue to develop interpretable AI methods for transcriptomic analysis to advance biomarker discovery and improve understanding of AD pathogenesis.

Proposed One-Year and Long-Term Outcomes:

For Aim 1, we will continue our imaging analysis methodology and pipeline development efforts, generate high-quality image analysis results for local and publicly accessible cohorts. We anticipate generating one or two publications in the upcoming year. For Aim 2, we anticipate generating two manuscripts on the application of deep learning models in ADRD research and exploring extramural funding opportunities in collaboration with Drs. Wang and Wu. For Aim 3, we will provide regular data release of image analysis results from our ongoing analysis efforts and support grants development to investigators inside and outside of our consortium.

Year End Progress Summary:

For Aim 1, we continue to develop image analysis methodologies to facilitate the early detection and characterizing disease progression. One direction that we have been working on in the past year focused on the development and evaluation of an improved longitudinal graph-based approach for tracking tau propagation using dynamic time warping (DTW) applied to serial tau PET scans. The method integrates multiple imaging timepoints to better characterize the temporal progression of tau pathology and generates graph-based metrics that distinguish cognitively unimpaired, mild cognitive impairment, and Alzheimer's disease participants. The longitudinal graph measures demonstrated improved sensitivity compared with conventional longitudinal tau PET metrics and identified an optimized composite region that substantially reduced estimated sample sizes for detecting treatment effects in preclinical Alzheimer's disease clinical trials. These findings support the utility of the DTW-based graph approach for monitoring tau progression and improving clinical trial design. We are currently preparing a manuscript based on this work. In

addition to methodology development, we also continue to expand our curated imaging datasets with standardized preprocessing and analysis to facilitate AD/ADRD research. The curated datasets have increased to 45k+ MRI scans, 16k+ amyloid PET, 7k+ tau PET from over 20k participants.

For Aim 2, we continue to develop ML/AI techniques for AD/ADRD research. In collaboration with Dr. Jing Li's team at Georgia Institute of Technology, we developed BrainPath, a deep learning framework that predicts subject-specific brain aging trajectories by generating anatomically faithful MRI scans at arbitrary past or future timepoints from a single baseline MRI. Trained on longitudinal ADNI data and validated on an independent NACC cohort, BrainPath integrates novel age calibration, swap learning, and age perceptual loss functions to model biologically meaningful structural brain changes while preserving individual anatomy. The framework outperformed a state-of-the-art brain age transformation method in image fidelity, temporal accuracy, and cross-dataset generalizability, while accurately reproducing regional brain volumes relevant to neurodegeneration. These results demonstrate BrainPath's potential to improve longitudinal assessment of brain aging, enable personalized disease monitoring, and support Alzheimer's disease and related dementia research by addressing the limitations of sparse longitudinal imaging data. This work is currently under review for publication. In another collaboration with Drs. Qi Wang and Teresa Wu at ASU, we developed an interpretable deep learning framework to identify molecular mechanisms underlying Alzheimer's disease (AD) using large-scale postmortem brain RNA sequencing data from the AMP-AD consortium. The framework employed multilayer perceptron models and SHAP (SHapley Additive exPlanations) analysis to classify AD across multiple brain regions while revealing biologically meaningful transcriptomic signatures associated with disease progression. The approach identified shared molecular pathways linked to microglial activation across brain regions and uncovered sex-specific neuronal gene networks, including a previously unrecognized role for the transcription factor pair ZFX/ZFY that may contribute to the greater neurodegeneration observed in women with AD. The models demonstrated strong performance in independent external cohorts and provided interpretable insights into region-specific and sex-dependent molecular changes, highlighting the potential of explainable artificial intelligence to accelerate biomarker discovery and therapeutic target identification for Alzheimer's disease (Trivedi et al., NPJ Aging 2025, PMC12267417). Supported in part by these research, we submitted two NIH grant proposals and one DOD AZRP proposal in the past year, while continue supporting Dr. Wang's R21AG091567 project.

For Aim 3, we continue to support collaborators in Arizona on AD/ADRD related research including collaborative research leveraging the large curated datasets described in Aim 1, while also provide our imaging and analytical expertise to consortium investigators.

References:

Trivedi MR, Joshi AM, Shah J, Readhead BP, Wilson MA, **Su Y**, Reiman EM, Wu T, Wang Q. Interpretable deep learning framework for understanding molecular changes in human brains with Alzheimer's disease: implications for microglia activation and sex differences. NPJ Aging. 2025;11(1):66. Epub 20250716. doi: 10.1038/s41514-025-00258-5. PubMed PMID: 40670382; PMCID: PMC12267417.

Yifan Li, Javad Sohankar, Ji Luo, Jing Li, **Su Y**. BrainPath: Generating Subject-Specific Brain Aging Trajectories. arXiv preprint arXiv:250816667v1. 2025. doi:10.48550/arXiv.2508.16667.

BANNER ALZHEIMER'S INSTITUTE - TUCSON
PROJECT PROGRESS REPORTS

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Clinical Profiles and Predictors of Cognitive Performance in Plasma P-tau217 Positive Individuals in Memory Clinic and Research Settings. Emily C. Edmonds, PhD, Steven Z. Rapcsak, MD, Dev Ashish, PhD, Marisa Menchola, PhD, Nicholas Ashton, PhD. Banner Alzheimer's Institute – Tucson; University of Arizona; Midwestern University; Banner Alzheimer's Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

Aim 1. To characterize the spectrum of cognitive impairments associated with p-tau217 positivity in a real-world memory clinic sample and identify medical/neurological comorbidities, and demographic factors responsible for variations in clinical severity and neuropsychological profiles.
Aim 2. To examine the clinical correlates of p-tau217 positivity in an Alzheimer's Disease Research Center (ADRC) sample and determine whether a combination of blood-based and imaging biomarkers of Alzheimer's disease (AD) and comorbid non-AD pathology improves prediction of disease stage and cognitive profile compared to p-tau217 alone.

Background and Significance:

Based on the literature, p-tau217 has good sensitivity and specificity for diagnosing AD and discriminating it from other neurodegenerative diseases. However, preliminary data in our clinic at Banner Alzheimer's Institute-Tucson (BAI-T) show limited associations between p-tau217 and clinical stage/severity (MCI vs. dementia) or cognitive profile (amnestic vs. non-amnestic). Our findings may reflect the fact that although p-tau217 is strongly associated with beta-amyloid pathology, it is a less accurate measure of the aggregated tau pathology that shows the strongest correlation with clinical symptom severity and cognitive profile. In addition, p-tau217 positive individuals meeting biological criteria for AD may harbor comorbid non-AD pathologies (e.g., vascular disease) that dominate the clinical picture. The clinical manifestations of p-tau217 positivity may also be influenced by demographic factors and medical/psychiatric comorbidities. The overarching goal of this project is to further characterize the clinical profiles of p-tau217 positive individuals and to identify predictors of cognitive performance within both a real-world memory clinic and a well-characterized research sample.

Preliminary Data, Experimental Design and Methods:

Aim 1 of the project is innovative in that it will be conducted in our BAI-T memory clinic sample which includes patients with medical and psychiatric comorbidities. This is a divergence from the more homogeneous samples often used in research studies and is a critical next step to understand biomarker association in real-world clinical settings. All patients will have subjective memory concerns; inclusion criteria include completion of neuropsychological battery at baseline, and availability of p-tau217 data. Aim 2 utilized the extensive clinical and biomarker data available within the Arizona ADRC to explore relationships with p-tau217 across the broader clinical spectrum of normal cognition to dementia. Extending biomarker research from the ADRC to clinical populations is an important step for informing the utility of biomarker profiles on clinical decision-making, which is critical as plasma p-tau217 biomarkers are becoming increasingly available to providers in clinical settings. A retrospective review of records was conducted, as well as ongoing record review for new patients seen in our memory clinic and new participants enrolled in the ADRC during the study period.

Proposed One-Year and Long-Term Outcomes:

Data generated from this project will lead to a scientific manuscript(s) and presentations at a scientific conference. Findings will be instrumental for future grant applications aimed at further

understanding the relationship between AD biomarkers, cognitive performance, and clinical outcomes in older adults, and how biomarkers and cognitive performance can be integrated into clinical decision-making regarding who is an ideal candidate for clinical trials and for treatment with anti-amyloid therapies.

Year End Progress Summary:

Progress was made on all specific aims, one-year outcomes, and long-term outcomes during the funding period. This included peer-reviewed publications, scientific presentations, and funded collaborations with researchers both within and outside of the Arizona Alzheimer's Consortium.

Aim 1: We examined the concordance of a clinical diagnosis of AD based on neuropsychological data and a biological diagnosis of AD based on p-tau217 positivity in 199 patients from our memory disorders clinic. Results showed that 61% (n=122) of the patients demonstrated a "classic" AD profile and the etiology of the patients' cognitive symptoms determined to be consistent with AD (either as the primary etiology or a major contributor to a mixed etiology). The other 39% (n=77) demonstrated a non-AD profile, due to either being cognitively normal or showing impairments that were more consistent with vascular disease, another neurogenerative condition (DLB, FTD), or a psychiatric condition.

Of the 122 patients with an AD profile, 100 (82%) also had a positive p-tau217 test (using a cutoff of 0.18 pg/ml), indicating concordance; however, 22 (18%) were biomarker negative and thus appear to represent individuals with conditions that mimic AD (e.g., LATE). Of the 77 patients with a non-AD profile, 33 (43%) were also p-tau217 negative, indicating concordance. However, 44 (57%) of the patients with a non-AD profile were found to be p-tau217 positive. This discordant group includes both cognitively normal individuals (n=12) with preclinical AD ("silent" pathology), as well as cognitively impaired patients who have biological evidence of AD, yet AD pathology does not appear to be driving their clinical symptoms.

Findings highlight the value of integrating neuropsychological and biomarker data when determining diagnosis and clinical stage. Specifically, neuropsychological data can detect cognitive impairment, but will be inaccurate at determining etiology in some cases due to AD mimics. On the other hand, biomarkers can detect AD pathology, but p-tau217 positive individuals will span the range from cognitively normal to those with a classic AD profile or a non-AD profile. Considering these unique sources of data together provides an optimal method for determining diagnosis, clinical stage, and underlying pathology. Additionally, further research is needed to explore biomarkers of vascular disease and other non-AD pathologies, particularly in the subset of patients who show a discrepancy between their biomarker and neuropsychological results.

Aim 2: Plasma p-tau217 has good sensitivity and specificity for detecting Alzheimer's disease (AD) pathology, but previous work shows that it may not provide information about clinical relevance or stage. We examined the relationship between p-tau217, cognition, and amyloid and tau PET imaging in the Arizona ADRC cohort. 507 participants (mean age=74.7 years; mean education=15.9 years; 61% female; 78% non-Hispanic white) from the Arizona ADRC completed p-tau217 testing and neuropsychological assessment. Consensus diagnoses included normal cognition (n=369), impaired-not-MCI (n=15), MCI (n=76), and dementia (n=47). A subset (n=86) also had amyloid and tau PET scans available. We examined correlations between p-tau217 level, neuropsychological test scores, amyloid PET Centiloids, and tau PET SUVRs. Area under the curve (AUC) analysis examined the ability of p-tau217 to predict amyloid and tau PET status.

Results showed that mean p-tau217 levels were significantly higher in participants with MCI and dementia (0.76-0.78 pg/mL) compared to normal cognition and impaired-not-MCI (0.45-0.48 pg/mL; $p<.001$). After controlling for demographic variables, p-tau217 level was negatively correlated with tests of global cognition, memory, language, attention, and executive functioning. Importantly, in cognitively impaired participants (MCI/dementia), p-tau217 was specifically related

to the cognitive domains typically affected in AD (i.e., episodic memory and semantic memory/language). In the full sample, there were significant positive correlations between p-tau217 level and amyloid PET Centiloid scores (r=.557) and tau PET SUVRs in entorhinal (r=.634) and meta-temporal (r=.600) ROIs (all p<.001). The correlations between p-tau217 and entorhinal and meta-temporal tau SUVRs remained significant after controlling for the association between p-tau217 and amyloid PET lesion burden (r = .423 to .445, p<.001). Furthermore, p-tau217 performed well in a binary classification model predicting amyloid and tau PET status with AUCs ranging from .747 to .827. Additionally, episodic and semantic memory measures were both correlated with amyloid PET Centiloids and tau PET SUVRs.

Findings suggest that p-tau217 is predictive of clinically symptomatic cognitive impairment with an AD neuropsychological profile. However, p-tau217 does not distinguish clinical stage (i.e., MCI vs. dementia), highlighting the value of integrating neuropsychological and biomarker data. Consistent with the literature, results in our Arizona ADRC cohort suggest that p-tau217 may be used not only to detect AD pathology (Core 1 biomarker) but also to provide information about the topography (Braak stage) and magnitude of tau lesion burden important for biological staging (Core 2 biomarker) and closely related to cognitive impairment.

Conference presentations during the funding period:

Edmonds, E. C. (September 2025). *Objective criteria for subtle cognitive decline in aging and preclinical Alzheimer's disease: A systematic review.* Invited presentation at the Arizona Alzheimer's Consortium's 26th Annual Scientific Conference, Tempe, AZ.

Edmonds E. C. (February 2026). *Objective approaches to identifying subtle cognitive decline in aging and preclinical Alzheimer's disease*. Symposium presented at the 54th meeting of the International Neuropsychological Society, Philadelphia, PA. (Symposium co-chair & speaker.)

Abstracts submitted for the 2026 Arizona Alzheimer's Consortium Scientific Conference:

Edmonds, E. C., Siu, H., Traslavina Jimenez, J., Grilli, M. D., & Rapcsak, S. Z. (September 2026). Relationship between p-tau217, cognition, and PET imaging in the Arizona ADRC.

Crisler-Kearney, A. S., Pachecho, D., **Edmonds, E. C.**, **Menchola, M.**, & **Rapcsak, S. Z.** (September 2026). Performance of plasma p-tau217 to detect Alzheimer's pathology in a clinical cohort with logopenic primary progressive aphasia.

Manuscript submitted during the funding period (collaboration with University of Arizona):

Hall, J. D., Liu, Y., Green, J., Hickey, R., **Edmonds, E. C., Rapcsak, S. Z.**, & Chou, Y. (2026). Identifying cognitive subgroups in older adults from community data with hierarchical cluster analysis. *Revised manuscript under review.*

New grants and collaborations during the funding period:

Awarded NIH grant: *Optimizing semantic memory measures of Alzheimer's disease biomarkers* (RF1AG093527). Drs. Edmonds and Rapcsak are co-investigators on this newly funded grant, which is a collaboration with the University of Arizona. The project examines relationships between AD biomarkers and semantic memory by integrating novel cognitive assessment, comprehensive neuropsychological assessment, structural MRI, and plasma p-tau217.

Resubmitted NIH grant. *Comparing Neuropsychological Approaches for Detecting Subtle Cognitive Decline in Older Adults.* Dr. Edmonds is MPI on a recently resubmitted R01, which is a multisite collaboration. The project will compare methods of defining subtle cognitive decline and examine associated clinical and biomarker outcomes. Results will have implications for enriching clinical trials and improving early detection in the pre-MCI phase.

Submitted AAC grant. *Concordance between Biological and Clinical Diagnosis/Staging of Alzheimer's Disease in Research, Memory Clinic, and Primary Care Cohorts.* Scientific Project Proposal submitted to the Arizona Alzheimer's Consortium; PIs: Drs. Edmonds and Rapcsak.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Partnering with Primary Care for Clinical Implementation of Blood-Based Biomarkers to Facilitate Early Detection and Access to Disease-Modifying Treatments for Alzheimer's Disease. Steven Z. Rapcsak, MD, Marisa Menchola, PhD, Emily C. Edmonds, PhD, Dev Ashish.
Banner Alzheimer's Institute – Tucson; University of Arizona; Midwestern University; Arizona Alzheimer's Consortium.

Specific Aims:

1) To build an enduring partnership between Banner Alzheimer's Institute-Tucson (BAI-T) and El Rio Health, one of the largest primary care networks in Southern Arizona, to facilitate early diagnosis of Alzheimer's disease (AD) in primary care by integrating p-tau217 biomarker testing into clinical practice and improve timely access to disease-modifying treatments (DMTs).
2) To educate El Rio healthcare providers (HCPs), as well as the patient populations they serve, about the availability and appropriate use of p-tau217 for early detection of AD and provide information about approved DMTs (lecanemab/donanemab) and clinical trials/research studies conducted at BAI-T.
3) To incorporate p-tau217 into a standard AD screening protocol to be administered in El Rio primary care clinics to individuals 55-years-old and older presenting with cognitive complaints and provide the opportunity for HCPs to consult with a BAI-T dementia specialist to assist with interpretation of test results and clinical decision-making.
4) To develop clinical guidelines and implement an efficient pathway for referring El Rio patients who screen positive for AD to BAI-T for further diagnostic work-up to determine eligibility for approved DMTs or clinical trials/research studies.
5) To identify and mitigate barriers to the clinical implementation of p-tau217 in a primary care setting and establish a new model of collaboration between community HCPs and dementia specialists to improve healthcare delivery and patient outcomes for AD.

Background and Significance:

Plasma p-tau217 has shown excellent sensitivity/specificity for diagnosing AD with important implications for early detection, prognosis, and treatment. Studies have shown that many patients with mild cognitive impairment (MCI) or early dementia due to AD are undiagnosed or misdiagnosed in primary care settings. Due to the failure to identify AD as the cause of cognitive symptoms, the majority of eligible primary care patients currently do not have timely access to DMTs at the early stages of the disease when these interventions are most likely to be effective. There is an urgent need to educate HCPs working in community primary care clinics, as well as the patient populations they serve, about the diagnostic potential and appropriate use of p-tau217, and to integrate these tools into clinical practice to identify individuals with early stage AD and facilitate prompt referral to specialty clinics for DMTs. Our proposal to establish a partnership between BAI-T and El Rio Health, one of the largest primary care networks in Southern Arizona, represents an important step toward addressing these healthcare challenges.

Preliminary Data, Experimental Design and Methods:

To accomplish the specific aims of our project, we propose to:

1) Provide a series of presentations to El Rio HCPs about the role of p-tau217 in early diagnosis of AD and appropriate use recommendations for approved DMTs (lecanemab/donanemab).
2) Implement an initial AD screening protocol to be administered in El Rio primary care clinics to individuals 55-years-old and older presenting with memory complaints that includes p-tau217 testing and a brief cognitive assessment (MMSE). In addition, El Rio HCPs will be offered the

opportunity to consult with a BAI-T dementia specialist to discuss interpretation of p-tau217 test results for individual patients and receive assistance with clinical decision-making.

3) Develop clinical guidelines and criteria for referring appropriate El Rio patients to BAI-T for further diagnostic work-up, determining eligibility for approved DMTs, and potential participation in the ADRC and clinical trials/research studies. In general, appropriate referrals to BAI-T will include p-tau217 positive individuals with an MMSE score of 20 or higher who may be at the MCI or early dementia stage of the AD continuum and therefore potentially qualify for DMTs or clinical trials. All referrals from El Rio will be triaged by the PI, and patients meeting criteria will be scheduled for an initial evaluation at BAI-T. Neuroimaging studies (MRI, amyloid PET), APOE4 genetic testing, and brief neuropsychological evaluations (in English or Spanish) will be scheduled by BAI-T. After completing the required work-up, eligible patients will be offered DMTs or participation in ADRC and clinical trials/research studies with continued follow-up at BAI-T.

Proposed One-Year and Long-Term Outcomes:

An important goal for our project is to improve early diagnosis of AD in primary care clinics by educating HCPs about p-tau217 and incorporating biomarker testing into the initial screening of individuals with cognitive impairment. To evaluate the effectiveness of our program, we will track the number of AD screening evaluations performed by El Rio HCPs in one year, the number of p-tau217 tests ordered, and the number of negative and positive test results. We will also track the number of new AD diagnostic codes entered into the El Rio EMR for the duration of our project compared to the one-year time period prior to the initiation of our screening program. To evaluate the effectiveness of our clinical pathway for primary care referrals to BAI-T, we will track the number of p-tau217 positive El Rio patients referred in one year, the number of patients qualifying for and receiving DMTs, and the number of patients entered into clinical trials or observational research studies (ADRC). We will also track clinic wait times for new El Rio referrals and the time required from initial evaluation to the start of DMTs. Our proposed one-year outcome is to complete the work-up and initiate DMTs for approximately 10-12 El Rio patients, and to begin the screening/enrollment process for 6 additional patients into clinical trials/research studies. With respect to long-term outcomes, our project will help identify and mitigate barriers to the implementation of p-tau217 biomarker testing in primary care settings and improve coordination of AD clinical care between community HCPs and BAI-T. Our program is expected to significantly improve timely access to DMTs not currently available to the majority of primary care clinic patients with early stage AD which, in the long-term, translates into better healthcare outcomes. The information gained from this project will help BAI-T design the optimal strategy for managing the anticipated surge in specialty clinic referrals for DMTs associated with the widespread use of p-tau217 in primary care clinics and provide an opportunity to establish a new model of AD care in the Tucson community. In addition to addressing an urgent clinical need, our project will provide valuable scientific and public health information about the impact of p-tau217 testing in real-world populations, including the prevalence of biologically defined AD in the Tucson community and the influence of medical/psychiatric comorbidities and demographic diversity on test results. Our plan is to use the data collected in this project for scientific publications comparing the performance of p-tau217 in primary care settings (El Rio) to memory disorders clinic populations (BAI-T) and research cohorts (ADRC).

Year End Progress Summary:

We made significant progress on all specific aims, one-year outcomes, and long-term outcomes during the funding period.

1) **Education Provided to El Rio Healthcare Providers**
   We provided two online lectures to El Rio primary care HCPs addressing the role of p-tau217 in early AD diagnosis and appropriate use recommendations for DMTs. These online presentations had a wide reach and were attended by approximately 80 physicians and nurse practitioners within the El Rio Healthcare network. In addition, we provided the opportunity for HCPs to consult with a BAI-T dementia specialist to assist with interpretation of test results and clinical decision-making on a case-by-case basis.
2) **Clinical Implementation of Plasma p-tau217 Biomarker Testing to Improve Early Diagnosis and Access to DMTs for AD**
   We successfully implemented an AD screening protocol for individuals 55 years and older presenting with memory complaints to El Rio primary care clinics that included p-tau217 testing and brief cognitive assessment (MMSE). Prior to implementation, no p-tau217 tests were ordered by El Rio HCPs. Since the start of our project, 246 tests have been ordered and 144 completed, with a 53% positivity rate for AD pathology. The p-tau217 positivity rate for AD in El Rio clinics represents a significant improvement over published clinical detection rates for early stage AD in primary care settings. Prior to the start of our project, no patients were referred to BAI-T from El Rio for DMTs. Following implementation of our clinical referral pathway, 28 El Rio patients were evaluated at BAI-T to determine eligibility for DMTs, 4 have qualified, 2 declined, and 12 are completing the required workup. Ten patients were found ineligible due to MRI exclusion criteria, medical comorbidities, or advanced dementia. Two of these individuals were subsequently offered enrollment into the ADRC. BAI-T wait times for El Rio referrals were reduced to 2 months compared to the community standard of 3-12 months. In summary, our project significantly increased AD diagnostic accuracy in a primary care setting by incorporating p-tau217 testing into the initial evaluation of patients with memory complaints and developed appropriate clinical guidelines and an expedited referral pathway between El Rio Health and BAI-T for timely access to DMTs. Our partnership represents an important step toward reducing disparities in access to improved AD diagnosis and treatment in underserved Hispanic populations and provides a new model of AD care in the Tucson community.

Conference presentations during the funding period:
Traslavina Jimenez, J., Soltani, L., Singh, P., Siu, H., Edmonds, E., Ashish, D., Menchola, M., & Rapcsak, S.Z. (May 2026). *Clinical Partnership for Implementing Blood-Based Biomarkers to Improve Early Diagnosis and Access to Disease-Modifying Treatments for Alzheimer's Disease.* Poster presented at the 2026 Southwestern Primary Care Research & Innovation Summit, Tucson, AZ. **(Winner of the "Best Overall Poster" Award)**

Abstract submitted to the 2026 Arizona Alzheimer's Consortium Scientific Conference:
Traslavina Jimenez, J., Soltani, L., Singh, P., Siu, H., Edmonds, E., Ashish, D., Menchola, M., & Rapcsak, S.Z. *Clinical Implementation of P-tau217 Blood Biomarker Testing in a Primary Care Setting to Improve Early Diagnosis and Access to Amyloid Targeting Treatments for Alzheimer's Disease.*

Grant proposal submitted:
Edmonds E.C., Rapcsak S.Z. (PIs), Ashish D., Menchola, M. (Co-I) *Concordance between Biological and Clinical Diagnosis/Staging of Alzheimer's Disease in Research, Memory Clinic, and Primary Care Cohorts.* Scientific Project Proposal submitted to the Arizona Alzheimer's Consortium.

BANNER SUN HEALTH RESEARCH INSTITUTE
PROJECT PROGRESS REPORTS

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

A Resource of Alzheimer's Disease Fluid Biomarker Expertise and Assays for Researchers in the Arizona Alzheimer's Consortium. Nicholas J. Ashton, PhD, Taina Marques, PhD. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

The primary aim of this initiative is to support two investigator-led projects, each awarded up to $60,000, to leverage advanced fluid biomarker platforms at the Banner Sun Health Research Institute Biomarker Laboratory. Through this targeted funding, the program seeks to catalyze impactful research aligned with the mission of the Arizona Alzheimer's Consortium (AAC) by advancing both discovery and translational applications of biofluid biomarkers in Alzheimer's disease and related dementias (ADRD).

Each selected project will receive:

- Full analytical support, including assay design consultation, sample processing, and biomarker quantification across cutting-edge platforms such as Simoa, Cobas, Lumipulse, and NULISA.
- Access to biomarker expertise, including assay validation strategies, study design input, and data interpretation assistance from the Banner biomarker team.
- Platform and matrix flexibility, enabling applicants to explore plasma, serum, CSF, or alternative biofluids as appropriate for their research aims.

By funding one project under the explorative track and one under the implementation track, the program will support a balanced portfolio of biomarker research-from novel target identification to applied integration in trial or clinical settings. The overarching goal is to generate high-impact data that can (1) inform future large-scale validation studies or funding applications, and (2) accelerate the clinical readiness and utility of fluid biomarkers in contexts and populations representative of Arizona.

Background and Significance:

The Fluid Biomarker Laboratory at Banner Sun Health Research Institute (BSHRI) serves as a centralized resource for the discovery, development, and implementation of fluid-based biomarkers in Alzheimer's disease and related dementias. Under the direction of Dr. Nicholas Ashton, an internationally recognized leader in neurodegenerative biomarker research, the laboratory has rapidly become a hub for both academic and industry collaborations.

The laboratory is equipped with state-of-the-art technologies for high-throughput biomarker measurement, including:

- **Fully automated immunoassay platforms** (e.g., Roche Cobas e801, Fujirebio Lumipulse G1200, Siemens Atellica, Beckman Coulter DxI 9000)
- **Ultra-sensitive detection systems** such as the Quanterix Simoa HD-X
- Next-generation multiplex discovery platforms, including NULISA (Next-Generation Ultra-Sensitive Immunoassay) with dual Argo systems
- Integrated capacity for **plasma, serum, CSF**, and alternative biofluid processing

The lab leads multiple national and international efforts to validate and standardize blood-based biomarkers—particularly phosphorylated tau (p-tau217)—and is a recognized leader in comparative assay evaluation, biomarker harmonization, and clinical assay implementation. It

also plays a central role in the biomarker infrastructure for the Alzheimer's Prevention Initiative (API), NIH-funded research consortia, and partnerships with biotech and pharmaceutical companies. Importantly, the laboratory maintains a dual research-service mission: it supports hypothesis-driven academic research while also operating under clinical-grade protocols that allow rapid translation of findings to real-world contexts. As part of Banner Health's broader mission, the lab is uniquely positioned to support accessible and scalable biomarker solutions that benefit patient populations representative of Arizona across the care continuum. As part of its commitment to the Arizona Alzheimer's Consortium (AAC), the lab provides prioritized access to assay platforms, technical expertise, and collaborative support to empower AAC investigators in advancing innovative, biomarker-driven research.

Preliminary Data, Experimental Design and Methods:

In 2024, with support from AAC funding, the Biomarker Laboratory funded three pilot projects at $30,000 each. These awards were granted to investigators at Mayo Clinic, Banner Alzheimer's Institute Tucson, and Arizona State University. All projects have been completed, and we are currently awaiting feedback from the investigators regarding their findings. A key takeaway from this inaugural call is that while the interest was strong, the funding level limited the scope of proposed work. To encourage more ambitious and impactful science, we have increased the funding per project and reduced the total number of awards in this cycle.

Proposed One-Year and Long-Term Outcomes:

Key Dates and Process for AAC Fluid Biomarker Awards (2025):

- RFP Announcement: August 2025. Consultation Period: Open by appointment following RFP release
- Letter of Intent (1 page) Due: September 26, 2025. Each LOI will receive feasibility feedback from the Biomarker Laboratory
- Full Proposal (3 pages) Due: November 26, 2025
- Award Announcement: December 12, 2025

Year End Progress Summary:

During the 2025–2026 reporting period, the Arizona Alzheimer's Consortium (AAC) Fluid Biomarker Resource continued to expand access to state-of-the-art fluid biomarker technologies for investigators across Arizona. Building on the success of the first funding cycle, the program further strengthened its role as a centralized resource for advanced biomarker analyses, collaborative study design, and technical expertise through the Banner Sun Health Research Institute Fluid Biomarker Laboratory.

The second AAC Fluid Biomarker Award competition was conducted during this reporting period. Based on experience gained from the first funding cycle, the program was redesigned to maximize scientific impact. Whereas the inaugural call funded three pilot projects at $30,000 each, the second call awarded two larger projects of up to $60,000 each. This change was made to enable investigators to undertake more comprehensive biomarker studies with greater statistical power and stronger potential to generate preliminary data for future NIH and foundation grant applications. Although five applications were received, representing a modest reduction in submissions compared with the first funding cycle, the overall scientific quality of the proposals remained high. All applications underwent rigorous independent external peer review by experts in neurodegenerative biomarkers, clinical neuroscience, and translational research. Applications were evaluated on scientific significance, innovation, methodological rigor, feasibility, investigator

expertise, and anticipated scientific impact, with the two highest-ranked proposals selected for funding.

The first funded project, led by Dr. Craig Weinkauf at the University of Arizona, aimed to investigate inflammatory pathways linking asymptomatic extracranial carotid artery disease (aECAD) with Alzheimer's disease risk. The proposal builds on compelling evidence demonstrating that individuals with carotid atherosclerosis have an increased risk of Alzheimer's disease and neurofibrillary pathology despite remaining clinically asymptomatic. The investigators hypothesized that endothelial inflammation associated with vascular disease contributes to blood-brain barrier dysfunction and represents an early mechanistic pathway leading to Alzheimer's disease pathology.

To address this hypothesis, the study utilized a well-characterized longitudinal vascular cohort comprising more than 200 participants with detailed clinical, imaging, cognitive, and plasma biomarker data. Using the NULISA Inflammation Panel, the project quantified a broad range of inflammatory proteins to determine whether endothelial inflammatory pathways differ between participants with and without carotid disease, whether these inflammatory signatures are modified following carotid endarterectomy, and whether inflammatory changes are associated with plasma p-tau217 concentrations and cognitive performance. By integrating advanced proteomic profiling with vascular imaging and Alzheimer's disease biomarkers, the study aims to identify mechanistic links between vascular disease and neurodegeneration while informing potential therapeutic strategies for dementia prevention.

The second funded project, led by Dr. Robert Bowser at Barrow Neurological Institute, investigated inflammatory protein signatures in matched plasma and platelet samples from individuals with Alzheimer's disease, C9-associated amyotrophic lateral sclerosis/frontotemporal dementia (ALS/FTD), and healthy controls. The proposal recognizes that systemic inflammation is a shared feature across multiple neurodegenerative diseases and that platelets represent a biologically informative but relatively underexplored source of peripheral biomarkers because of their central role in immune signaling and inflammatory mediator release.

Using the ultra-sensitive NULISA Inflammation Panel, the project sought to define the relationship between inflammatory proteins measured in platelets and plasma collected from the same individuals. The study aims to identify platelet-derived inflammatory signatures that are detectable in plasma, determine their relationship with clinical measures of disease and cognition, and evaluate their potential as minimally invasive biomarkers for neurodegenerative disease. Comparisons across Alzheimer's disease, ALS/FTD, and healthy control participants are expected to provide insight into both shared and disease-specific inflammatory mechanisms while informing future plasma biomarker development.

Following award selection, the Banner Sun Health Research Institute Fluid Biomarker Laboratory worked closely with both investigative teams to finalize analytical plans, coordinate sample transfer, perform quality control procedures, and complete biomarker measurements using standardized laboratory workflows. All biomarker analyses have now been completed, and comprehensive quality-controlled datasets have been returned to the collaborating investigators for downstream statistical analysis and biological interpretation.

At the time of this report, we are awaiting the investigators' analyses and reporting of their findings, including manuscripts, conference presentations, and future grant applications arising from these pilot studies. The results generated through these projects are expected to provide important

preliminary data supporting larger externally funded studies while further strengthening collaborative biomarker research across the Arizona Alzheimer's Consortium.

Overall, the second AAC Fluid Biomarker Award cycle demonstrated the continued value of the AAC Fluid Biomarker Resource in supporting innovative, investigator-led research across Arizona institutions. The transition from three smaller pilot awards to two larger awards enabled more comprehensive and ambitious biomarker studies while leveraging the advanced analytical capabilities of the Banner Sun Health Research Institute Fluid Biomarker Laboratory. Although the number of applications was modestly lower than during the first funding cycle, the scientific quality of the submissions remained high. To further expand the reach and impact of the program, we plan to increase awareness of future funding opportunities through enhanced promotion at the Arizona Alzheimer's Consortium Annual Meeting, together with broader communication across AAC institutions and investigator networks. We anticipate that greater visibility will increase participation in future funding rounds, foster new collaborations across the Consortium, and broaden the use of advanced fluid biomarker technologies by Arizona investigators. As blood-based biomarkers continue to move toward clinical implementation, the AAC Fluid Biomarker Resource remains well positioned to provide investigators with access to cutting-edge technologies, standardized analytical pipelines, and expert scientific support that will accelerate biomarker discovery, validation, and translation for Alzheimer's disease and related dementias.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

DROP-AD: A capillary blood test for Alzheimer's disease pathology. Nicholas J. Ashton, PhD, Alireza Atri, MD, PhD, Thomas Beach, PhD, Geidy Serrano, PhD. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

1) Aim 1: Evaluate analytical correlation between capillary and venous pTau217 measurements Compare pTau217 levels from matched capillary DPS samples (Telimmune and Drawbridge) and venous EDTA plasma in 75 participants using Simoa assays. Assess correlation, agreement, and classification accuracy.
2) Aim 2: Optimize and compare capillary blood collection platform performance Evaluate Telimmune and Drawbridge DPS cards for pTau217 quantification, focusing on yield, reproducibility, sample integrity, and inter-device agreement using standardized workflows.
3) Aim 3: Establish SOPs and assess remote use feasibility Develop platform-specific SOPs for capillary sample collection, elution, and analysis. Evaluate participant adherence, sample quality, and processing success rates for remote/unsupervised deployment.

Background and Significance:

Blood biomarkers for Alzheimer's disease (AD), particularly phosphorylated tau-217 (pTau217), have rapidly evolved into clinically valuable diagnostics with superior accuracy for detecting cerebral amyloid-β pathology, offering cost-effective identification of individuals likely to benefit from AD therapies. While current guidelines recommend testing only symptomatic patients, evidence supports preclinical screening where earlier intervention may improve outcomes and enhance equitable access across diverse populations. Commercial immunoassays now rival immunoprecipitation-mass spectrometry performance, yet logistical barriers persist: venipuncture requires trained personnel, immediate processing, and cold-chain logistics, limiting population-level screening and real-world implementation. The DROP-AD project addresses these challenges by evaluating capillary blood collection via dried plasma spot (DPS) cards—a decentralized, minimally invasive method eliminating venipuncture, centrifugation, and cold-chain transport, potentially enabling home self-collection. Building on prior work showing variable results and high collection failures with capillary blood, we assess upper arm capillary collection feasibility, comparing pTau217 and NfL from DPS samples to matched EDTA plasma to benchmark this remote collection method for AD screening.

Preliminary Data, Experimental Design and Methods:

We evaluated the feasibility and diagnostic performance of capillary blood collection via dried plasma and blood spot (DPS/DBS) cards for measuring Alzheimer's disease (AD) biomarkers across seven European sites (n=313). Capillary pTau217 levels showed strong correlation with venous plasma ($r_s = 0.74$) and high discriminative accuracy for abnormal CSF biomarkers (AUC = 0.863). GFAP and NfL measured from capillary samples also correlated well with plasma values ($r = 0.77$ and 0.83, respectively) and cognitive status. In individuals with Down syndrome, capillary pTau217 and GFAP levels aligned with clinical and CSF measures. Importantly, unsupervised self-collection was feasible, and yielded biomarker results comparable to supervised collection. These data support the utility of decentralized, remote blood biomarker testing for AD and related disorders.

Year End Progress Summary:

DROP-AD 2.0 builds upon the successful proof-of-concept established in the original DROP-AD study, which demonstrated that Alzheimer's disease (AD) blood biomarkers can be accurately measured from remotely collected capillary blood. While the first study established the feasibility of decentralized testing using dried plasma spot (DPS) technology across multiple international sites, DROP-AD 2.0 is designed to overcome the remaining barriers to widespread implementation. Specifically, we will evaluate next-generation upper-arm capillary blood collection devices that improve collection reliability, increase plasma yield, and enhance patient usability in unsupervised home settings. By comparing two optimized collection platforms against matched venous plasma using clinically validated pTau217 assays, this study aims to establish a robust, scalable workflow for remote Alzheimer's disease biomarker testing. Successful completion of DROP-AD 2.0 will provide the analytical and operational evidence required to support large-scale population screening, longitudinal disease monitoring, and decentralized clinical trials.

DROP-AD 2.0 successfully recruited 87 participants (60 [67.0%] female; mean [SD] age, 76.8 [8.4] years), all of whom completed blood collection using multiple remote capillary collection devices in addition to a standard venous blood draw. This paired-sample design enables direct comparison of remote collection technologies with conventional plasma sampling for the measurement of AD blood biomarkers. Participant demographics and the number of successful collections for each blood collection device are summarized in Table 1 . Blood biomarkers were measured on range of platforms including; cobas® e 801 platform (Roche Diagnostics), the Nucleic Acid Linked Immuno-Sandwich Assay (NULISA™) CNS panel and the Janssen p-tau217+ immunoassay (HD-X, Quanterix)

Our primary biomarker of interest was plasma phosphorylated tau 217 (p-tau217), a highly accurate biomarker of Alzheimer's disease pathology. Using the reference standard assay (cobas® e 801 platform, Roche Diagnostics), 36.1% of participants were classified as having high p-tau217 concentrations (≥0.326 pg/mL), 26.5% as intermediate (0.201–0.326 pg/mL), and 37.4% as low (≤0.201 pg/mL). This distribution ensured representation across the full spectrum of AD biomarker status for evaluating remote blood collection technologies. Consistent with previous reports, only a weak correlation was observed between venous and Tasso+ levels of p-tau217 when measured directly ($R = 0.28$, $p = 0.011$, Figure 1A). Similar weak correlations and elevations in Tasso+ samples were observed for p-tau181, p-tau231, and brain-derived (BD) p-tau biomarkers. Our most notable finding was that the BD-p-tau217/BD-p-tau181 ratio from Tasso+, which demonstrated a robust correlation with venous Roche p-tau217 concentrations ($R = 0.76$, $p < 2.2 \times 10$-16, Figure 1B). In contrast, neurofilament light (NfL) ($R = 0.95$, $p < 2.2 \times 10$-16, Figure 1C) and glial fibrillary acidic protein (GFAP) ($R = 0.96$, $p < 2.2 \times 10$-16, Figure 1D) showed excellent agreement between venous and Tasso+ plasma without the need for normalization or ratio-based approaches. Out of all 131 biomarkers probed, 47 (35.9%) had a Pearson R greater or equal to 0.90. In total, 29 biomarkers (22.1%) had Pearson R values between 0.70 and 0.90, 25 (19.1%) had values between 0.30 and 0.70, and 30 (22.9%) had values less than 0.30 (Figure 2)

After spotting venous plasma onto Telimmune DUO cards and subsequently extracting the plasma, we observed a strong correlation between venous plasma and venous Telimmune plasma (Figure 2A; $R=0.80$, $p<2.2\times10^{-16}$). This demonstrated a robust extraction procedure from DPS. This shows potential for using Telimmune DUO cards to circumvent centrifugation and cold-chain shipping of venous plasma. A moderate association between venous plasma and Capitainer SEP 10 DPS plasma (Figure 2B; $R=0.32$, $p=0.02$) was observed, which is slightly weaker than correlations demonstrated in previous studies. However, no relationship between venous plasma and Tasso Telimmune DPS plasma (Figure 2C; $R=0.0024$, $p=0.98$) was found.

DROP-AD 2.0 successfully demonstrated the feasibility of evaluating next-generation remote blood collection technologies for AD blood biomarker testing in a well-characterized cohort of 83 participants. Consistent with the original DROP-AD study, the findings confirm that remote capillary blood collection can support accurate measurement of several neurodegenerative biomarkers. Importantly, this study highlighted that biomarker performance is dependent on both the collection device and the analytical assay. While direct measurement of p-tau217 from Tasso+ plasma showed only modest agreement with matched venous samples, the brain-derived (BD)-p-tau217/BD-p-tau181 ratio substantially improved concordance, demonstrating that optimized analytical approaches can overcome matrix-related differences. The dried plasma card (DPS) platform demonstrated weak analytical performance. Together, these results indicate that both optimized upper-arm collection devices provide viable approaches for decentralized biomarker testing, although the optimal platform may vary according to the biomarker being measured. Most importantly, DROP-AD 2.0 has catalyzed the next phase of decentralized biomarker research. The analytical and operational insights generated by this study have directly informed the design of a substantially larger validation study that will evaluate next-generation remote blood collection devices across a broader and more diverse population. This future study will assess longitudinal performance, user acceptability, and clinical implementation, providing the evidence required to deploy remote blood biomarker testing for population screening, decentralized clinical trials, and routine clinical care. Collectively, DROP-AD and DROP-AD 2.0 establish a clear roadmap toward scalable, home-based Alzheimer's disease biomarker testing.

DROP-AD 2.0 has catalyzed the formation of an international working group on remote blood biomarker testing, led by Taraneh Atri (BSHRI), to advance best practices and accelerate the implementation of decentralized AD biomarker research. Preliminary findings have been presented to the Arizona Alzheimer's Consortium, with additional presentations planned for the Alzheimer's Association International Conference (AAIC 2026) and the Clinical Trials on Alzheimer's Disease (CTAD 2026) conference. A draft manuscript describing the analytical performance and clinical feasibility of the remote blood collection platforms is currently in preparation and is expected to be submitted for publication in Summer 2026.

Table 1.

Characteristic	Value
Age (years)	76.6 ± 8.4
Female (n (%))	60 (67.0)
APOE4* (n (%))	15 (17.2)
CU (n (%))	69 (79.3)
MCI (n (%))	10 (11.5)
AD (n (%))	8 (9.2)
Low p-Tau217 (n (%))	31 (37.4)
Intermediate p-Tau217 (n (%))	22 (26.5)

High p-Tau217 (n (%))	30 (36.1)
Capitainer cards with 0 blue circles (n (%))	30 (34.5)
Capitainer cards with 1 blue circle (n (%))	40 (46.0)
Capitainer cards with 2 blue circles (n (%))	17 (19.5)
Tasso volume too low for analysis (<25 µL) (n (%))	4 (4.6)

Figure 1.

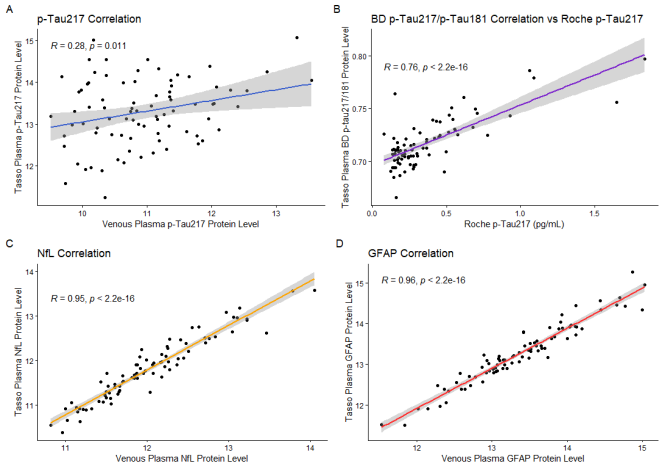


Figure 2.

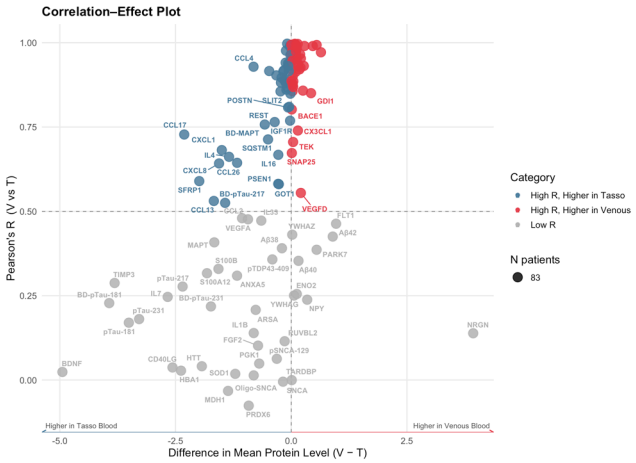
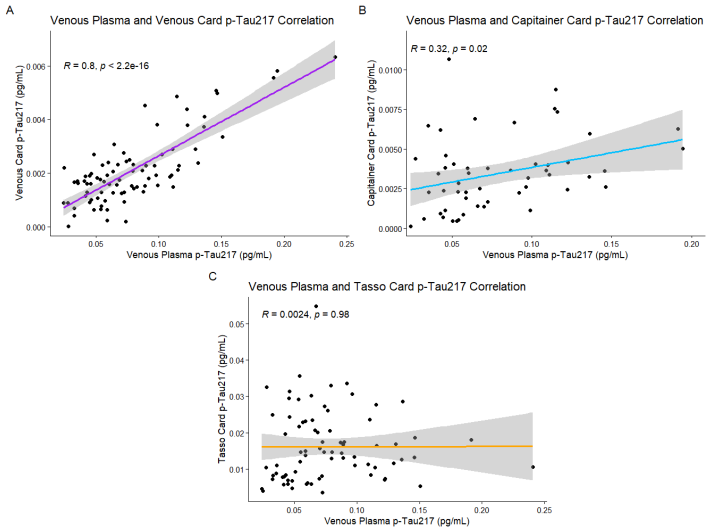


Figure 3.



ARIZONA ALZHEIMER'S CONSORTIUM
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Development, Validation and Implementation of Cognitive and Clinical Composites for the Arizona Study of Aging and Neurodegenerative Disorders/BBDP. Alireza Atri, MD, PhD, Michael Malek-Ahmadi, PhD, Parichita Choudhury, MD, Christine Belden, PsyD, Andrew Ho, DO, Thomas Beach, PhD, Geidy Serrano, PhD, Jessica Langbaum, PhD, Matt Huentelman, PhD, Kewei Chen, PhD. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Arizona State University; Translational Genomics Research Institute; University of Arizona College of Medicine; Arizona Alzheimer's Consortium.

Specific Aims:

4) Overarching AIM/AIM 1: Develop, validate and implement a global cognitive composite (GCC) for the Brain and Body Donation Program (BBDP)/Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) that includes multiple standard neuropsychological domains.
5) AIM 2: Utilize AIM 1 to develop global clinical (staging/global severity) and clinical domain-specific composites for the BBDP/AZSAND that includes composites of activities of daily living (ADLs), behavior/neuropsychiatric domains and sensorimotor functions (validation and extension AIM)
6) AIM 3: To utilize AIM 1 to explore the nature of the impact of neuropathological entities (e.g. individually, additively, synergistically), particularly vascular brain changes, on cognitive domains and composite latent variables, using machine learning (ML) and structural equation modeling (SEM) methods (implementation and exploratory AIM).

Background and Significance:

The world-renowned BBDP contains a rich and unmatched clinico-pathological dataset that is being enriched with structural, metabolic (PET) and fluid (cerebrospinal fluid and blood samples) biomarker data. The BBDP is responsible for seminal research findings in cognitive aging, Alzheimer's disease (AD) and related disorders, and AD biomarker validation; has accounted for >600 publications; and consistently accounts for >50 scientific publications and supports >50 grants annually. Participants receive standardized general medical, neurological, cognitive, neuropsychological, behavioral/neuropsychiatric, global clinical (cognitive-functional staging), and movement disorders assessments during life and more than 90% receive full pathological examinations after death.

Since 1996, while some BBDP tests have remained constant (e.g. the Mini-Mental Status Exam – MMSE), others have not. These include many domain-specific neuropsychological tests; as well as global staging assessment (e.g. Functional Assessment Scale, Global Deterioration Scale, Clinical Dementia Rating scale). The MMSE is the global brief cognitive test most available longitudinally where autopsy data is also available and thus has been used as the general proxy for "cognition" (and even global cognitive-functional or dementia staging) when assessing clinico-pathological relationships in BBDP projects. However, due to MMSE's relatively blunt nature as cognitive test designed to detect dementia-level impairment (it is insensitive to detect mild cognitive impairment, MCI, and subject cognitive decline, SCD, in educated participants) this has led to insensitivity to explicate clinico-pathological, age-, and disease-specific relationships with global cognition, and specific neuropsychological domains (e.g. attention, memory, language, executive functions, visuospatial cognition).

Preliminary Data, Experimental Design and Methods:
We used BBDP data from participants with autopsy data and at least one cognitive and clinical assessment in the data base. We assessed, catalogued (including timeframes/spans) and classified cognitive tests and measures used since the inception of the BBDP/AZSAND and found 88 cognitive tests and summary or global measures and assessments were utilized over 25+ years. We classified these into 8 different domains that include global/summary measures (e.g. CDR, DRS, MMSE, MoCA) and 7 cognitive domains (Attention/Concentration, Orientation, Memory, Language, Executive Functions, Processing Speed, and Visuospatial/Perceptual). We explored PCA, ML (including artificial neural network, ANN) and structural equation modeling (SEM) approaches using pilot areas to better understand clinico-pathological associations and co-variance structures in the data and the research question areas (AD/LBD pathology cognitive profiles; MCI clinical stage; Vascular Brain Changes in MCI).

One-Year and Long-Term Outcomes:
Developing composites appropriately-suited to the BBDP/AZSAND will substantially increase our ability to maximally harness the power of this important AZ-based and internationally-renowned study and to greatly enhance its impact in the coming years to explicate neuropath-biomarker-clinical relationships, and to accelerate the pace of biomarker and therapeutic approaches to better treat, slow, and, eventually, to prevent, AD and ADRD.

One-Year Outcomes:
1) Iterative refinement, assessment and improvement of preliminary global (and domain-specific) cognitive composite(s) for BBDP/AZSAND (AIM 1);
2) Utilizing approaches to cognitive composite as a template to explore and iteratively develop composites for other domains (of cognition, daily function, neuropsychiatric/behavioral, sensorimotoric) (AIM 2);
3) Exploratory assessment of composite and domain-specific approaches in MCI (AIM 3; see preliminary data);
4) Presentation of 2 abstracts in scientific meetings;
5) Publication of one manuscript

Long-Term Outcomes:
Long-term outcomes of achieving all three aims of this project, including iterative development, implementation and validation through multiple clinicopathological research questions and projects will factorially increase the impact of this important AZ-based and internationally-renowned study, and our AZ Consortium; leading to an even higher number of impactful publications (currently ~30-40 per year), greater grant funding, and further investment, support and development of public-private partnerships, scientific programs and biotechnology in AZ.

Year End Progress Summary:
We have made excellent progress to set the foundations for achieving all aims. We preprocessed data from participants with autopsy data and at least one assessment that included MMSEs, neurologic, neuropsychological, and movement exams. Clinicopathologic diagnosis available included 418 cognitively unimpaired controls (CU), 935 with AD, 257 with PD, 171 with DLB, 182 with Vascular Dementia, 82 with Hippocampal Sclerosis, and 54 with FTLD-TDP. We catalogued and classified 88 cognitive and summary/global tests/measures used since BBDP inception into 7 cognitive domains and 8 different global domains. We then developed a Long Short-Term Memory (LSTM) based neural network to predict cognitive and diagnostic outcomes across multiple visits that aims for primarily norm construction for composite scores in “Normal” (CU) versus “Abnormal” cognitively impaired (CI) status. Baseline characteristics for n=1257 subjects were for CU (n=969) and CI (n=288) diagnoses with mean±SD respectively

were: age 76.3±7.9 vs 78.0±7.4 years; %female 37.1% vs 67.5%; education 15.4±2.7 vs 14.7±2.9 years; and %APOE-e4 carrier 20.5% vs 35.7%.

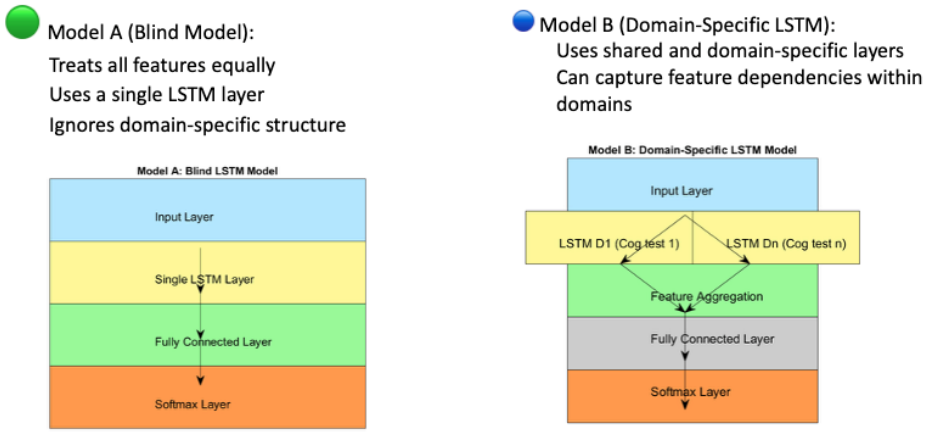


Figure 1. Long Short-Term Memory (LSTM) based neural network (Figure 1) to predict cognitive and diagnostic outcomes across multiple patient visits. The main model outcome is the Softmax layer which creates the norm for CU vs CI classes.

Domain-specific composites approaches include empirically derived and cross-validated, and multivariate statistical techniques such as principal component analysis (PCA). We primarily use empirically derived and cross-validated approaches, including iteratively exploring machine learning (ML) approaches, especially artificial neural network (AAN) approaches prioritizing Interpretability. We built a preliminary LSTM based neural network model towards achieving AIM 1 with good accuracy (0.864 for Model-A and 0.852 for Model-B) of predicting CU vs CI classification across the first 10 BBDP visits. Other approaches to be considered include exhausted search on the mean-to-standard-deviation ratios (MSDRs), seeking the optimal composition which best discriminate the baseline group difference between neuropathologically different groups (e.g. CU, AD, PD, DLB), and use of PCA for composite score formation, which can be domain specific (e.g. where PCA component 1 is memory specific and component 2 executive function specific). These experiences and modelling approaches can be applied to assess AIM 2 of developing corresponding composites for global, staging and clinical domains. Concurrently, in exploratory AIM 3 the impact of multiple neuropathological changes (NPCs), with a particular focus on interactions between AD neuropathologic changes and vascular brain injury, Lewy Body NPCs and TDP-43 NPCs will be explored to expand our work on the MCI clinical construct, profiles and domains/composites.

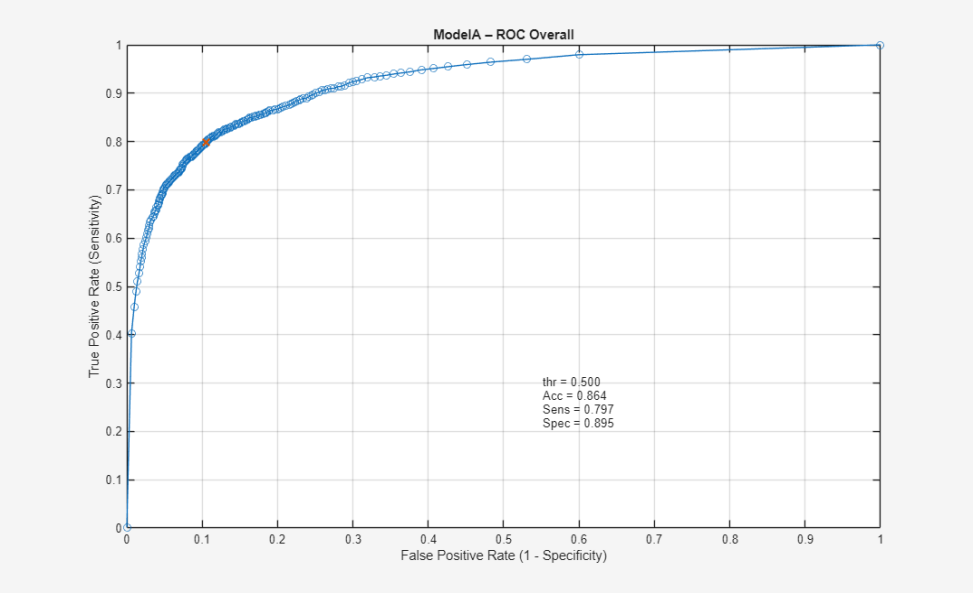


Figure 2. Receive Operator Characteristic (ROC) for LSTM Model-A based neural network to predict cognitive and diagnostic outcomes across the first 10 BBDP visits, yielded an accuracy of 0.864, sensitivity of 0.797 and specificity of 0.895. The ROC for LSTM Model-B (not shown) yielded similar results: accuracy 0.852, sensitivity 0.779 and specificity 0.886.

We continue to make excellent progress at achieving the project goals.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Clinical Phenotyping and Biological Characterization of The Longevity Cohort Study: Global Staging and Biospecimen Banking. Alireza Atri, MD, PhD, Michael Malek-Ahmadi, PhD, Geidy Serrano, PhD, Christine Belden, PsyD, Thomas Beach, PhD, David W Coon, PhD, Matt Huentelman, PhD, Kewei Chen, PhD. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

1) **Clinical research phenotyping**, via global staging of participants, through use of an algorithm to identify and administer the Clinical Dementia Rating (CDR) scale assessment to study participants and their study partner in individuals at higher risk of cognitive impairment and dementia (CID).
2) **Blood collection and biospecimen banking** of 30 cc of plasma from study participants to be made available for collaborative research opportunities and for preliminary data investigations for grant applications; and referral and co-enrollment of participants in other cognitive aging and biomarker studies.
3) **Delineating characteristics and biopsychosocio-environmental determinants of successful aging**. Utilize advanced mathematical methods, including machine learning (ML), to identify and validate detection and predictive measures, and patterns of biopsychosocial and clinical characteristics that support successful aging (cognition, function behavior and satisfaction) in the oldest old.

Background and Significance:

In its 18th year, "**The Longevity Study: Learning from Our Elders Cohort" (LCS) is a biopsychosocial study of longevity and successful aging, particularly in the oldest-old (aged 85+)**. The LCS provides critical multimodal clinical data and biospecimens to accelerate collaborative and cutting-edge research to link bio- and psychosocial factors in the study of successful aging. These data and biospecimens, and co-enrollment and referral of participants to impactful cognitive aging and biomarker studies, will create a synergistic effect of adding value and impact potential for an enhanced LCS database with a range of quality biopsychosocial data in a unique population, the older and the oldest old.

LCS participants are annually assessed to characterize cognitive and psychosocial trajectories to discern patterns of successful aging and delineate subclinical cognitive impairment and (very mild) dementia (CID). We refer and co-enroll participants with the Brain and Body Donation Program (BBDP), allowing further deep clinical phenotyping and biological characterization (e.g. MRI, CSF, PET scans, brain donation with neuropathological characterization), and with other studies to support AAC and AZ ADRC projects and grant proposals. Shared samples and biodata readily linked to psychosocial and cognitive variables collected in the LCS is contributing to advances in blood-based biomarkers (e.g. DROP-AD: developing a capillary blood test for AD).
This proposal aims to continue obtaining, sharing, and analyzing data and samples to enhance collaborative research and funding opportunities and improve vital aging and advance dementia prevention science.

This study aims to continue obtaining, sharing, and analyzing data and samples to enhance collaborative research and funding opportunities and improve vital aging and advance dementia prevention science.

Preliminary Data, Experimental Design and Methods:
The LCS has 575 active participants (enrolled 1,792 since inception; 68% female) with 96% annual retention. The average age is 79±10 (SD) (Median = 80) years; 55% (323) are ≥ 80; 13% are ≥ 90 years of age; at least 78 are between 90-99, and 7 are 100 years or older. We have published important cognitive normative data in the oldest-old (90+) (Melikyan et al.) where there had been a literature gap.

One-Year and Long-Term Outcomes:
We expect to add to prior progress by further longitudinal clinical phenotyping of participants; continuing collection, characterization and biobanking of additional plasma samples (added to samples from active and past participants) from newly enrolled and returning participants; and contributing to scientific progress in aging and ADRD.

One-year goals:
1) Add at least 40 new participants,150 CDRs and 300 plasma samples to LCS;
2) At least 150 referrals and co-enrollments with allied studies of aging and ADRD (especially to the BBDP/AZ SAND study, DROP AD 2.0+);
3) Sharing data and biosamples with AAC/ADRC investigators to support research projects/grant proposals;
4) Support at least 3 new neuroscience summer scholar interns and projects;
5) Submit/resubmit for publication research manuscripts and NIH grants (led by Drs. Malek-Ahmadi, Schaefer and Ashton); 4 grants currently under review or in resubmission;
6) Samples with Dr. Ashton's lab for biomarker discovery and development, including for the DROP AD;
7) Continue steady referrals of participants to clinical research and trial programs.

Longer term impactful outcomes for this project: In addition to accumulation of short-term outcomes, we plan to prepare additional presentations and submit publications and proposals to fund grant applications from foundations, state and federal agencies (e.g. NIH).

Year End Progress Summary:
There has been excellent progress on the grants aims during the funding year 2025-26.

Aim 1 summary of progress made in 2025-26: Met/exceeded goals - obtained 202 CDR (96 BBDP-co-enrolled) and 266 plasma samples. Of active participants, 96% are without dementia, and incidence of minimal/mild cognitive changes/impairments is ~25% (within expected range given age demographics).

Aim 2 summary of progress made in 2025-26: Met/exceeded goals - banked more than 1168 plasma samples and shared >1083 of 0.5ml plasma samples with Dr. Ashton's BSHRI Fluid Biomarker Program Labs to facilitate discovery research including for Dr. Ashton and for Dr. Schaefer's AAC) and AZ ADRC REC fellows developmental grant project (334 have NULISA analysis and 973 have pTau-217 and Ab-42 data).

Aim 3 summary of progress made in 2025-26: Dr. Atri collaborated with Dr. Kewei Chen, Dr. Malek-Ahmadi and other AAC investigators (including Drs. Serrano, Belden, Choudhury, Ho) to explore a variety of ML analyses utilizing BBDP longitudinal cohort data. Application and validation of ML methods is an ongoing aim.

In 2025-26 the LCS data and grant supported multiple poster presentations (including at AAC annual research conference) and grant applications. There were/are three grants in

submission/resubmission. Dr Schaefer (PhD, ASU, Assoc. Professor AAC/ADRC developmental grant recipient) and Dr. Beeman – “Identification of neurobiological mechanisms of the Brief Evaluation of Daily Living and CognitioN (BEAN) for early AD screening”, R01; and “Characterizing the timing and microstructural basis of motor deficits in AD using MRI, R01. Dr. Malek-Ahmadi: “Plasma TDP-43 Associations with Age-Related Subjective Cognitive Complaints and Neurodegeneration”, R01. >500 LCS BEAN tests have been performed. Supported DROP-AD (Dr. Ashton AAC grant) with 80 participant referrals, and his lab with >200 blood samples. There were multiple presentations at regional, national and international conferences including the Alzheimer’s Association International Conference.

Successful participant referral/enrollment in AAC/ADRC research studies contributing to clinic-neuropathological correlation and biomarker validation in AD/ADRD. We had 96 active co-enrolled LCS-BBDP participants, >60 deceased/donated brains; and, in last several years, >700 referrals from LCS/CHA to research programs, including >200 to BBDP, NIA-AZ-ADRC and clinical trials.

We continue to make excellent progress at achieving these goals.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Shared Resource of Research Participants Data and Biological Samples for Study of Alzheimer's Disease. Alireza Atri, MD, PhD, Thomas Beach, MD, PhD, Parichita Choudhury, MD, Andrew Ho, DO. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Specific Aims:

1) Aim 1: to support specific efforts to help with ongoing participant recruitment, data, brain and body tissue collection and resource sharing as part of the Arizona Alzheimer's Consortium ADRC and affiliated programs.
2) Aim 2: to forge innovative and impactful multi-institutional, multi-disciplinary collaborations, to provide shared resources, and to collaborate with other institutions to ensure the development of sufficient infrastructure for the rapid enrollment of AD and ADRD studies.

Background and Significance: The Arizona Alzheimer's Consortium (AAC) is widely recognized as a model of multi-institutional collaboration in biomedical research. It capitalizes on complementary resources and expertise from different disciplines and organizations to address scientific problems in the most impactful way. Our Arizona Alzheimer's Disease Research Center (AZ ADRC), and affiliated studies and programs, including The Brain and Body Donation Program (BBDP), form substantial infrastructure and cores for impactful multi-institutional, multi-disciplinary resources, collaborations, and programs for AD/ADRD basic, translational and clinical research. The AAC, ADRC and BBDP provide a world-leading scientific resource of longitudinal and neuropathological data, brain and body tissues for the study of AD, Parkinson's disease, and related disorders in their BBDP program. The program has increasingly incorporated ante-mortem biomarkers (including amyloid and tau PET scans, MRIs, cerebrospinal fluid, and blood-based biomarkers) and new brain tissue resources to help ADRD and brain researchers address their goals with even greater impact.

Preliminary Data:

Not applicable – This is a strategic proposal designed to enhance recruitment, increase collaborations, and ensure sufficient infrastructure for rapid enrollment into AD and ADRD studies (please see above Background section for the breadth and depth of activities, and Proposed One-Year and Long-Term Outcomes, below). While this project overlaps with the scientific goal and aims of the AZ ADRC Cores there is no budgetary overlap. The budget here equals the additional costs for personnel-leaders of the ADRC that are not supported by our NIH funds for these complementary consortium and related, affiliated and collaborative activities.

Experimental Designs and Methods: This proposal requests complementary support to enhance ongoing efforts for participant recruitment, data, brain and body tissue collection and resource sharing as part of the Arizona Alzheimer's Consortium ADRC and affiliated programs.

Aim 1: to support specific efforts to help with ongoing participant recruitment, data, brain and body tissue collection and resource sharing as part of the Arizona Alzheimer's Consortium ADRC and affiliated programs.

To help achieve this aim partial support is requested to:

a) perform standard evaluations and collect UDS and additional data on all participants, including a large number of Hispanic/Latino and Native American participants.
b) provide neuropathologic diagnoses and process, store and distribute postmortem brain tissue, including from those who provided blood samples in the last 1-2 years of their lives.
c) support and provide access to genetics, brain imaging (MRI, amyloid PET, tau PET), cerebrospinal fluid (CSF) and BBBs of AD.

Aim 2: to forge innovative and impactful multi-institutional, multi-disciplinary collaborations, to provide shared resources, and to collaborate with other institutions to ensure the development of sufficient infrastructure for the rapid enrollment of AD and ADRD studies.

To help achieve this aim partial support is requested to:

a) support necessary personnel to ensure the development of sufficient infrastructure for rapid enrollment into AD and ADRD studies.
b) Oversee outreach, education, recruitment projects such as the Brain Health Check In and community lectures to facilitate recruitment into studies.

Proposed One-Year and Long-Term Outcomes: The proposed outcomes would be to provide the shared resources needed to help advance the study, early detection, tracking, diagnosis, treatment and prevention of AD and related dementias, develop new research leaders, help find an AD prevention therapy as soon as possible, and establish the roles of blood-based and fluid biomarkers in these endeavors.

Year End Progress Summary: There has been outstanding progress in 2025-2026 toward the aims of the grant. The AAC, AZ ADRC, and BBDP remain highly productive, collaborative and impactful, leading regional, national and international scientific hubs for the collective effort to discover and advance diagnostics and therapies for AD/ADRD.

There was substantial collaboration, coordination and progress supported by this project that provided shared resources of research participants, data and biological samples for the study and advancement of research diagnostics and therapeutics in AD for the FY26 projects at BSHRI, which from 7/1/25-6/30/26 were: 1) Patient-based live cell banking for translational research (PI G. Serrano), 2) Clinical Trajectories, biomarkers and associations with pathology in Lewy body spectrum disorders (PI P. Choudhury), 3) Drop Alzheimer's Disease (DROP-AD) (PI N. Ashton), 4) Impact of Cholinesterase-Inhibitors on Clinical Trajectories, Milestones and Mortality in Autopsy-Supported Alzheimer's disease (PI A. Ho), 5) Enhancing Clinical and Biological Characterization of The Longevity Cohort Study: Global Staging and Biospecimen Banking (PI A. Atri), 6) Development, Validation and Implementation of Cognitive and Clinical Composites for the Arizona Study of Aging and Neurodegenerative Disorders/BBDP (PI A. Atri), and 7) A Resource of Alzheimer's Disease Fluid Biomarker Expertise and Assays for Researchers in the Arizona Alzheimer's Consortium (PI N. Ashton).

In support of AIMS 1 and 2, the internationally renowned BBDP, directed by Thomas Beach, MD, PhD (supporting by this project), and Geidy Serrano, PhD, continued its path in FY26 as a premier national and international research program by adding **132 new participant donors and conducting 3,480 annual assessments in 690 living participants.** Drs. Atri, Choudhury and Ho, supporting this project (AIMS 1 and 2), provided referral, assessment, oversight and leadership to achieve these BBDP metrics, including participant and collection and assessment of clinical research and imaging data and biosamples; and for referral, co-enrollment, assessment, and oversight participants in our AZ ADRC. In FY26, The BBDP

distributed over 206 transfers encompassing more than 30,000 biospecimens including shared samples with more than 80 Arizonan scientists (including more than 120 shipments to scientists other US states and internationally scientists); and contributed to >50 scientific publications; supported >60 grant-funded research projects and grant proposals; collected >50 skin biopsy samples, >500 blood samples and 45 cerebrospinal fluid samples, and more than 70 PET scans for amyloid plaques, tau tangles, synapses (SV2A) and/or structural brain MRI changes (>850 scans over the past 5 years at BAI Phoenix) from participants. **Over 200 BBDP participants are co-enrolled in the AZ ADRC's Clinical and Ancillary BBDP Cores and the ADRC's Neuropathology Core,** in partnership with Mayo Clinic AZ, Barrow Neurological Institute (part of the AZ ADRC clinical core through June 30, 2026), BAI Phoenix and BAI-Tucson (which moved organizationally to the University of Arizona in 2026). The BBDP also plays critical roles in the neuropathological validation of amyloid-, tau- and synaptic (SV2A)-PET and other ante-mortem biomarkers, contributing to assessment and FDA approval of molecular imaging/PET, CSF and blood-based biomarkers for AD/ADRD (see below); and provides a critical tissue resource for genome-wide genetic, transcriptomic and proteomic data from different brain regions and cell types, and to dozens of impactful research studies, collaborations, grants, and annual publications.

During the 2026 reporting period, the program also supported (AIMS 1 and 2) three PET-related studies with autopsy confirmation, including one focused on amyloid pathology, one on tau pathology (The Civin Lab at BSHRI is the Neuropathology Core for this national study and Dr. Atri is the global coordinating PI), and a third on synaptic density sponsored by the Foundation for NIH where BSHRI is the single site and Drs. Atri, Beach and Serrano are MPIs with Dr. Atri as leading the clinical and imaging and Drs Serrano and Beach leading the neuropathological assessments – during the reporting period 7 participants who had undergone full clinical, biofluid and neuroimaging assessments (brain MRI and SV2A synaptic brain PET scans) died and donated their brains for synaptic-PET-neuropathological correlations and validation. Additionally, Dr. Ashton's lab analyzed plasma samples from 51 participants who had also undergone SV2A-PET scans to assess correlations of synaptic PET with AD-related biomarkers including pTau-217. The totality of these results are supportive of the background evidence that is being prepared for submission of a NIH R01 (MPIs Drs. Beach, Serrano and Atri; Co-I's Drs. Choudhury, Su and Ashton) on October 5th, 2026, to continue this work to obtain longitudinal SV2A-PETs in this unique cohort (n=64 currently have obtained a full set of clinical/cognitive/dementia-related assessments, MRI and SV2A PET scans; target n is 75 by end of 2027). This R01 will support the validation of SV2A PET as a in vivo measure of brain synapse. Continuation of this work is expected to result in 15-20 more participants to come brain donation to definitively support SV2A PET-autopsy correlation and validation in the next 5-6 years. The BBDP program's established expertise and reputation in therapeutic- and biomarker-driven neuropathologic studies have additionally attracted interest from industry partners; notably, a new sponsor has approached BBDP regarding the collection and evaluation of brains from individuals treated with anti-amyloid therapies, requesting guidance during protocol development and expressing interest in BBDP serving as an active study site, reflecting the program's recognized leadership in treatment-related neuropathology and translational research.

The **BSHRI Fluid Biomarker Program, directed by Dr. Nicholas Ashton**, who is also Leader of the AZ ADRC Biomarker Core, now its third year, and with opening of their state-of-the-art laboratories in January 2021, has become an internationally recognized hub for the discovery, validation, and high-throughput analysis of blood and other fluid biomarkers for AD, PD, and related neurodegenerative conditions. This program was strongly supported by this shared

resource **(through AIM 2) including for its AAC project Drop Alzheimer's Disease (DROP-AD) (PI N. Ashton).** Novel capillary-blood collection methods have not yet been evaluated for a wide range of central nervous system (CNS) and neurodegenerative disease-related proteins. Biomarkers of AD/ADRD collected from devices like the Tasso+, a minimally invasive upper-arm capillary blood collection device widely used in research settings, must be compared to traditional venipuncture to assess for validity. Through support of this shared resource (especially through referrals from the Longevity Cohort Study and clinics by Drs. Atri, Choudhury and Ho), 83 older participants (age mean±SD 76.8±8.2 years, 79.5% cognitively unimpaired) underwent blood collection via traditional venipuncture and Tasso+ at BSHRI, and the Nucleic Acid Linked Immuno-Sandwich Assay (NULISA) CNS panel was used for biomarker quantification in venous and Tasso-derived plasma. Preliminary results of this important study were presented at The Alzheimer's Association International Conference (AAIC) (Atri TE et al. CTAD July 2026), and a paper has been submitted and under review for publication at this time (Atri TE et al. Performance of Upper-Arm Capillary Blood Collection for Alzheimer's Disease and Central Nervous System Biomarkers: Comparison of Tasso+ and Venous Plasma, Alzheimer's & Dementia: DADM, under review).

Additionally, in support of AIM 2, we have **more than 25 active AD/ADRD trials**, 129 screening visits, 111 successful randomizations, 12 new studies initiated in 2025/206 (6 new studies initiated in AD, 6 for Movement Disorders). Also, in support of AIM 2, referrals from Brain Health Fairs and outreach events, and the **Brain Health Check-In (BHCI) program** – a free community service & outreach program that **has served over 1392 individuals (247 individuals in 2026)** thus far were important for enrollment in our clinical trials, research cohorts and studies.

Supporting referral and assessment in our AZ ADRC, we have 2068 National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) assessed participants in our ADRC program, including 732 Actively followed Clinical Core participants (June 1, 2026, NACC UDS monthly report for our center), an additional 29 participants with Minimal Contact status, and 1307 participants in affiliated studies (Arizona APOE Cohort, BBDP, LEADS). In our active clinical core participants, 69% are classified as cognitively unimpaired, 13% as mild cognitive impairment (MCI), 13% as dementia, and 4% as impaired not-MCI/MBI. Notably, we have 191 currently enrolled Hispanic/Latino participants of whom 88 have complete and active data in the NACC UDS database. This shared resource has also facilitated support that contributes to a very high retention in our clinical core cohort of ~90% of our participants followed (retained) at 3 years, ~70% at 5 years, and ~45% at 10 years since initial visit.

This shared resource has also provided support to facilitate excellent ATN (Amyloid, Tau, Neurodegeneration)-related scan and biofluid acquisition with a high rate of participation and ADRC scans completed, and our strong contribution to the national ADRC-affiliated CLARiTI neuroimaging study – we met our imaging completion goals of a full set of brain MRI, amyloid and tau PET scans for 36 participants -- and to achieve the highest rate (~90%) of brain autopsy completions among all NIH Alzheimer's Disease Research Centers.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Clinical trajectories, biomarkers and associations with pathology in Lewy body spectrum disorders. Parichita Choudhury, MD, Kewei Chen, PhD, Thomas Beach, PhD, Charles H. Adler, PhD, Alireza Atri, MD, PhD. Banner Sun Health Research Institute; Mayo Clinic Arizona; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium; Arizona State University; University of Arizona; Translational Genomics Research Institute.

Specific Aims:

1) Aim 1: To use SEM to model how clinical impairments contribute to Lewy body pathology prediction and assess the modifying influence of Alzheimer's disease co-pathology.
2) Aim 2: Compare the predictive performance of a refined clinical-functional composite score with plasma and CSF biomarkers (e.g. α-synuclein Seed Amplification Assay (SAA), pTau217) for Lewy body pathology.

Background and Significance:

Lewy Body Disorders (LBD), encompassing Dementia with Lewy bodies (DLB) and Parkinson's Disease Dementia (PDD), represents a spectrum of α-synucleinopathies characterized by overlapping clinical and pathological features [1,2]. This overlap contributes to diagnostic uncertainty and misclassification [3,4]. Accurate in vivo detection of Lewy body (LB) pathology remains a major unmet need. While it is intuitive that greater symptom severity might correspond with higher pathological burden, studies have shown inconsistent associations. Moreover, individuals with incidental Lewy body disease (ILBD) can harbor significant pathology without clinical manifestations, suggesting variability in symptom expression due to individual differences in neural reserve or coexisting pathologies, particularly Alzheimer's disease (AD), which is commonly comorbid in LBD and may modify clinical features or biomarker profiles [5,6].

Advancements in synuclein-based biomarkers, such as α-synuclein seed amplification assays (SAA) in cerebrospinal fluid (CSF) and skin, have demonstrated promise in improving early detection [7–11]. However, fluid biomarkers alone do not fully capture the clinical complexity of LBD. To address this gap, **our group developed a data-driven clinical-functional composite that predicts LB pathological burden** using longitudinal clinical assessments from an autopsy-confirmed cohort integrating cognitive, motor, neuropsychiatric, and olfactory features [12].

While our preliminary composite demonstrates that multidomain clinical features can approximate underlying LB pathology, the mechanistic relationships among these domains remain unclear, particularly in the context of AD co-pathology. Furthermore, the relationship between molecular signatures in plasma and CSF, clinical composite scores, pathological burden, and sources of heterogeneity (e.g. sex differences) remains poorly defined.

Building on this prior work, the proposed studies will advance biological models of LBD by integrating proteomic biomarkers and explicitly examining heterogeneity in disease expression.

Experimental Designs and Methods:

Aim 1: We have prior results supporting the utilization of ML techniques/models to assess LB pathologic burden with key measures collected in relatively small samples. Across all these ML models, the smell test score UPSIT was the most influential predictor (>65% occurrence on the top ranking based on Shapley assessment), followed by Controlled Oral Word Association Test (COWAT) and age. We have also used SEM as a tool to investigate complex relationship between the set of variables in LBD clinicopathologic correlations. SEM combines regression analysis and factor analysis to create a framework to test hypothesized relationship incorporating latent variables, the cog (cognition), Mot (motor) and OlF (olfactory) as predictors and account for their measurement errors.

Subject Inclusion/Exclusion Criteria: Cases included in this analysis will span the entire spectrum of Lewy body pathologies in the AZSAND database (13): PD including PDD (n=277), DLB (n=189), Alzheimer's Disease with Lewy-type synucleinopathy (n=291) and ILBD (n=134). For Aim 1, cases will be excluded if only one measure is available and if interval between last assessment and death is greater than 2 years.

Clinical Scales: Demographic information will be included. Clinical features described in aggregate will include presence of REM sleep behavior disorder, cognitive fluctuations, visual hallucinations, autonomic dysfunction. In addition to demographic information, we will utilize several scales to explore a unified composite risk score. The following scales will be considered as components of Lewy body score: Mini Mental Status Exam (MMSE), Montreal Cognitive Assessment (MoCA), Clinical Dementia Rating Scale (CDR) global, CDR-Sum of Boxes (CDR-SB), Neuropsychiatric Inventory questionnaire (NPI-Q), Unified Parkinsons Disease Rating Scale (UPDRS-part 1), Mayo Sleep Questionnaire (MSQ), UPDRS- part 3, Functional Assessment Screening tool (FAST) and University of Pennsylvania Smell Identification Test (UPSIT).
Aim 2: We will leverage results from the Neuronal Synuclein Disease Endotypes Program to compare neurodegenerative markers and their clinical composites. Pre-collected samples will be used from a common cohort of cases from the BBDP/AZSAND. We will focus on cases with pathology-confirmed LBD, with at least one complete clinical and functional assessment prior to death. These cases will represent a range of Lewy body pathology, including ILBD, Alzheimer's disease with Lewy bodies (ADLB), DLB with or without coexisting AD, PD and PDD, in accordance with pathological consensus criteria of international DLB consortium and previous publications from our group (1,13). We will also include cases with pure AD pathology and those without major neuropathologic diagnoses (controls). Neurodegenerative markers assayed in the Neuronal Synuclein Disease Endotypes Program include CSF SAA, Abeta42/40, P-tau217, GFAP, NfL (in plasma and CSF).

Year End Progress Summary:
Overall, there was excellent progress in this project during FY 07/01/2025 – 06/30/2026, including a preliminary *SEM of clinicopathologic relationships with strong fit statistics, a plasma proteomic signature strongly associated with Lewy body pathological burden, and validation of postmortem CSF as a viable substrate for large-scale biomarker discovery*. Two manuscripts stemming from this work and another from a related project are currently in preparation, as detailed below.

Aim 1: We developed and evaluated ML models to assess LB pathologic burden using clinical, cognitive, and functional measures in an autopsy-confirmed cohort. Across models, the olfactory score (UPSIT) consistently emerged as the most influential predictor (>65% occurrence in top-ranking features), followed by Controlled Oral Word Association Test (COWAT) and age. We then implemented a structural equation modeling (SEM) framework incorporating cognition (Cog), motor (Mot), and olfactory (OlF) domains as latent variables. The model demonstrated excellent fit (Chi-square p=0.285, RMSEA=0.0345, CFI=0.9913), supporting its validity for modeling complex clinicopathologic relationships. *This manuscript is currently undergoing edits by co-authors.*
Figure 1: Preliminary structural equation modelling incorporating clinical characteristics, such as cognitive, motor and olfactory functions to predict Lewy body staging

Plasma proteomic analyses demonstrated a strong association between a multi-protein integrated score and LB density ($R^2 = 0.92$, $p < 1\times10^{-30}$), supporting the biological relevance of circulating protein signatures in reflecting underlying pathology. Proteomic data in this cohort (n=61) were analyzed using a supervised neural network framework with 127 protein inputs and a single continuous output representing LB density. Given the modest sample size, model performance was evaluated using leave-one-out cross-validation (LOO-CV), ensuring that each subject served as an independent test case. This approach maximizes training data utilization while providing an unbiased estimate of predictive performance.

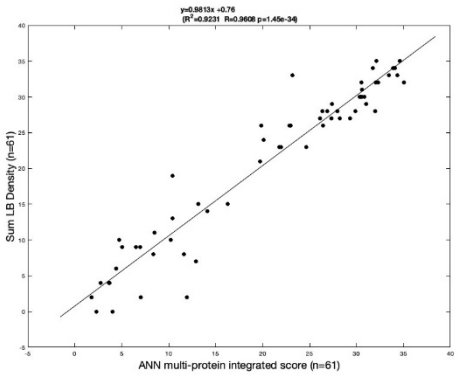


Figure 2: Plasma proteomic score shows strong correlation with Lewy body pathology burden.

In a complementary analysis, the proteomic model demonstrated good discriminative performance in distinguishing AD from LBD (AUC = 0.83), suggesting that plasma proteomics captures both disease-specific molecular signatures and within-disease pathological burden.

Aim 2: To support the planned large-scale postmortem CSF proteomics for biomarker discovery in this Aim, we have established the validity of postmortem CSF as a proxy for antemortem CSF using high-multiplex proximity-based immunoassay profiling. Thirty paired antemortem-postmortem CSF samples from a neuropathologically confirmed mixed cohort (Lewy body disease, Alzheimer's disease, and cognitively normal controls) were profiled across 127 targets using the NULISAseq CNS Disease Panel (Alamar Biosciences). Overall concordance was strong, with a **median Pearson r of 0.891 across 125 evaluable targets; 85 targets (68%) achieved r > 0.80**. Established neurodegeneration markers including NEFL, GFAP, phosphorylated tau species, and neuroinflammatory proteins showed near-perfect concordance (r > 0.99 for top correlators). *These results provide an empirical foundation for postmortem CSF proteomics and are being prepared for publication as a methods validation report. This validation step was a prerequisite for Aim 2's planned comparison of the clinical-functional composite with plasma and CSF biomarkers, including SAA and pTau217. α-synuclein SAA data are already available for this cohort as part of our companion autopsy-validation project, conducted under the MJFF Neuronal Synuclein Disease Endotypes Program; however, the direct comparison against the composite score has not yet begun, as proteomic profiling of the remaining CSF samples is still ongoing. Integration of biomarker data into a single refined clinical-functional composite (per our proposed one-year outcomes) will follow completion of this analysis.*

I also contributed as an author to two related publications this year: I served as second author on a longitudinal analysis of olfactory decline and its associations with cognitive decline and postmortem neuropathology (Tremblay et al., medRxiv, 2026), directly relevant to the olfactory domain of our Aim 1 composite, and co-authored a multisite validation of skin biopsy α-synuclein seed amplification assays for predicting Lewy body disease (Janarthanam et al., J Neuropathol Exp Neurol, 2026), relevant to the SAA biomarker comparison proposed in Aim 2.

Overall LBD research progress: In collaboration with colleagues at Mayo Clinic Arizona, we submitted a grant proposal to evaluate and compare multimodal biomarkers in Lewy body disease. While the proposal was not funded, we received encouraging reviews and are actively pursuing funding opportunities for resubmission. We continue to serve as one of the LBDA Research Centers of Excellence, having been renewed for another year, and are partnering with LBDA to host another community event. Over the past year, I have continued to build and lead a program of research focused on Lewy body disease, with particular emphasis on clinicopathological correlations, biomarker development, and sex differences in

neurodegeneration. I had the opportunity to present much of this work at national meetings this year: our SEM findings (Aim 1) were presented at AAN and Arizona Scientific Symposium, and our α-synuclein SAA-based Autopsy Validation of Biological Classification Framework developed as part of the MJFF Neuronal Synuclein Disease Endotypes study (Aim 2), together with our plasma proteomics findings on sex differences in Lewy body disease, were presented at AAIC 2026 (Platform presentations).

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Impact of Cholinesterase-Inhibitors on Clinical Trajectories, Milestones and Mortality in Autopsy-Supported Alzheimer's Disease. Andrew Ho, DO, Parichita Choudhury, MD, Alireza Atri, MD, Michael Malek-Ahmadi, PhD, Eric Reiman, MD. Banner Sun Health Research Institute; Banner Alzheimer's Institute; University of Arizona - College of Medicine, Phoenix; Arizona State University; University of Arizona (Tucson); Arizona Alzheimer's Consortium.

Specific Aims:

1) Aim 1: To assess and compare, in persons who at autopsy showed Alzheimer's disease neuropathologic changes (AD-NPC), differences in clinical characteristics and cognitive and clinical trajectories (e.g. MMSE, MoCA, cognitive domain scores and composite) between those exposed to ChEI treatment and those not exposed to ChEI treatment during the MCI stages of illness.
2) Aim 2: To assess the associations of ChEI treatment exposure on key clinical milestones in persons with MCI and AD-NPC including time to clinical progression (e.g. measured by Clinical Dementia Rating (CDR) global and sum-of-box scores), emergence or worsening of neuropsychiatric symptoms (e.g. Neuropsychiatric Inventory Questionnaire (NPI-Q)), changes in functional status (e.g. Functional Assessment Scale (FAS)), and rates and time to progression to severe disability or institutionalization.
3) Aim 3: To determine whether administration of ChEI to individuals with Alzheimer's disease during the MCI stages affects survival time.

Background and Significance:

Mild cognitive impairment (MCI), particularly the amnestic subtype, has been considered to represent, with high likelihood, a prodromal stage of Alzheimer's disease (AD). Given the high rate of progression from MCI to dementia stages of illness, ChEI have been studied for their potential to slow cognitive decline and delay clinical progression. While some clinical trials and real-world studies have reported modest short-term cognitive benefits in persons with MCI treated with the most widely used CHEI, donepezil, [2], these effects have not been consistently demonstrated or shown to translate into improved global functioning [1,3] or long-term disease course modification [4].

Previous research on donepezil and other ChEI involved individuals with the clinical AD dementia or AD MCI phenotype who met clinical criteria but did not require biomarker or neuropathological support for AD-NPC, leaving a critical gap in understanding regarding any potential utility of treatment in those with MCI and confirmed AD-NPC. A lack of biomarker or neuropathological support for AD-NPC and evidence to support AD as a driver (cause) of the MCI syndrome may have contributed to mixed results from past clinical trials and real-world studies regarding potential efficacy of ChEI treatment in MCI [10,14]; and potential beneficial responses may differ between individuals with AD versus non-AD causes of MCI [5,6,8,15].

With advances in biomarkers, it is now possible to detect amyloid and other neurodegenerative markers in vivo, allowing for accurate identification of persons with MCI that is likely to be driven by AD-NPC. ChEI are also now broadly accessible. As part of the treatment paradigm of AD there is great familiarity with ChEI in general medical practice; they are widely available at low cost with several generic formulations; and after decades of use in millions of persons, ChEI have well-established tolerability and safety profiles in real-world patient populations. A revisitation of the

question of the characteristic and potential efficacy of ChEI in MCI with AD-NPC is therefore timely and justified, and, if established, may be of great public health impact in the U.S. and globally. This study aims to evaluate whether exposure to ChEI treatment in autopsy-confirmed MCI cases with AD-NPC is associated with slower cognitive and clinical decline and beneficial impact on functional-span and survival. Leveraging a rich-set of longitudinal data from the NACC UDS database, this research will examine treatment-associated characteristics and outcomes in a pathologically enriched cohort, potentially informing a more targeted approach to early therapeutic intervention with ChEIs in MCI with AD-NPC. The outcomes of this project could support practice-changes, as current clinical guidelines regarding the use of ChEI in the MCI stage of AD remain inconclusive and lack clear consensus.

Preliminary Data, Experimental Design and Methods:

A comprehensive query of the NACC UDS database identified approximately 289 individuals with impaired cognition (MCI or Impaired-not-MCI) and autopsy-confirmed Alzheimer's disease neuropathologic change (AD-NPC) who were treated with cholinesterase inhibitors (ChEI) prior to dementia onset, along with over 800 untreated participants meeting study criteria. Cohort refinement includes validation of medication exposure, identification of treatment initiation dates, harmonization of longitudinal follow-up visits, and evaluation of diagnostic consistency across study visits. Additional methodological refinements, including review of longitudinal diagnostic transitions and exclusion of participants with inconsistent or implausible clinical trajectories, will strengthen the internal validity of the study.

Subject Selection:

The study will include individuals in the NACC UDS database with impaired cognition (MCI or Impaired-not-MCI) who were subsequently shown at autopsy to have intermediate or high Alzheimer's disease neuropathologic change (AD-NPC) according to NIA-AA criteria and who had at least two longitudinal study visits. Individuals with normal cognition at baseline, dementia at baseline, insufficient follow-up, missing key variables, or inconsistent longitudinal diagnostic trajectories will be excluded from the primary analysis. To maximize diagnostic specificity, analyses will be restricted to participants with neuropathologically confirmed Alzheimer's disease.

Groups and Data Extraction:

Participants will be categorized into two groups based on documented exposure to ChEI therapy prior to dementia onset: those who received donepezil, rivastigmine, or galantamine during the impaired cognitive stage (MCI or Impaired-not-MCI) and those who remained untreated. Dates of treatment initiation and discontinuation will be extracted when available. Demographic and clinical variables including age, sex, education, race/ethnicity, APOE ε4 status, family history, baseline cognitive performance, vascular risk factors, concomitant medications, and longitudinal clinical diagnoses will be collected. For treated participants, longitudinal analyses will be aligned to the first visit documenting ChEI exposure, while untreated participants will retain their initial study visit as baseline.

Outcome Measures:

The primary outcomes for the Aim 1 will explore changes in cognitive function as measured by the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), and a UDS battery cognitive composite scores over time. In Aims 2 and 3, outcomes for behavioral/neuropsychiatric symptoms, activities of daily living and global severity will be the Neuropsychiatric Inventory Questionnaire (NPI-Q) (and secondary will be Geriatric Depression Scale (GDS)); the Functional Activities Scale (FAS); and the CDR, respectively. Time to progression to CDR global milestones, severe disability (and minimal contact status in NACC

UDS), institutionalization, and all-cause mortality will be assessed by comparing the time (and assessing hazard ratios) from baseline to milestones between the ChEI and non-ChEI groups.

Statistical Analysis:
Longitudinal cognitive and clinical trajectories will be evaluated using linear mixed-effects models comparing treated and untreated participants over time. Fixed effects will include treatment group, time, and the treatment-by-time interaction, with random intercepts and slopes specified at the participant level to account for repeated observations. Covariates will include baseline age, sex, education, APOE ε4 status, baseline cognitive severity, vascular comorbidities, and concomitant psychotropic or cognitive-enhancing medications. Because treatment initiation occurred at variable times following enrollment into the NACC cohort, longitudinal follow-up for treated participants will be aligned to the first documented ChEI exposure, while untreated participants will retain their initial visit as baseline. Sensitivity analyses will evaluate the robustness of this approach and explore potential treatment-selection bias using propensity score-based adjustment or inverse probability weighting where appropriate.

Kaplan-Meier survival curves and Cox proportional hazards models will be used to evaluate time to dementia progression, severe disability, institutionalization, and all-cause mortality. Multivariable models will adjust for age, sex, education, APOE ε4 status, baseline cognitive performance, functional status, and relevant comorbidities. Censoring due to loss to follow-up will be accommodated, and subgroup analyses will examine treatment effects according to baseline cognitive severity and APOE ε4 status. Additional sensitivity analyses will evaluate the impact of early dementia conversion and alternative definitions of treatment exposure. This comprehensive analytic approach is designed to determine whether ChEI exposure prior to dementia onset is associated with improved cognitive trajectories, delayed clinical milestones, and prolonged survival in individuals with neuropathologically confirmed Alzheimer's disease.

Proposed One-Year and Long-Term Outcomes:
By July 2026, the following goals are anticipated to be accomplished:
1. Data collection and refinement of cohorts of MCI with underlying pathological diagnoses, and their pharmacological treatments.
2. Iterative development and MMRM and Cox-proportional hazards analysis and generation of cognitive and clinical trajectories and KM curves for milestones involved in AIMS 1-3.
3. Submission of an abstract to American Academy of Neurology and potentially a second one to Alzheimer’s Association International Conference.
4. Manuscript preparation for publication.
5. Long-term outcome, if supported by the results, would include preliminary results to support a Ph4 pragmatic trial grant application.

Year End Progress Summary:
During the first year of funding, substantial progress was made toward the overall objective of evaluating the association between cholinesterase inhibitor (ChEI) treatment during the mild cognitive impairment (MCI) stage of Alzheimer's disease and subsequent cognitive trajectories, clinical milestones, and survival in individuals with autopsy-confirmed Alzheimer's disease neuropathologic change (AD-NPC). The primary emphasis during this funding period was the construction of a rigorously defined longitudinal cohort, refinement of the analytic strategy, and preparation of high-quality datasets for statistical analysis.

Progress Towards Proposed One-Year and Long-Term Outcomes
1. Data collection and refinement of cohorts of MCI with underlying pathological diagnoses, and their pharmacological treatments.

The objective of cohort construction has been largely completed. Data extraction from the NACC Uniform Data Set linked with neuropathology was successful, and inclusion/exclusion criteria were refined to identify MCI participants with intermediate or high AD neuropathologic change at autopsy. The final cohort surpassed expectations, with around 289 ChEI-treated and over 800 untreated participants. Significant effort went into validating medication exposure, identifying treatment initiation dates, harmonizing follow-up visits, and ensuring diagnostic consistency. Methodological refinements, including reviewing longitudinal diagnostic transitions and excluding implausible trajectories, further enhanced internal validity.

2. Iterative development and MMRM and Cox-proportional hazards analysis and generation of cognitive and clinical trajectories and KM curves for milestones involved in AIMS 1-3.
Significant progress was made toward the proposed longitudinal and survival analyses through refinement of the statistical analysis plan to better account for the observational nature of the NACC dataset. Linear mixed-effects models were selected to evaluate longitudinal changes in cognitive, functional, and neuropsychiatric outcomes while accounting for repeated measures and relevant baseline covariates, including age, sex, education, APOE ε4 status, and baseline disease severity. During data preparation, substantial variability in the timing of ChEI initiation relative to participants' initial NACC visit was identified, prompting development of a revised analytic framework in which follow-up for treated participants is aligned with treatment initiation while untreated participants retain their initial visit as baseline. Sensitivity analyses are being incorporated to evaluate potential bias associated with this approach, and preparation of the longitudinal datasets required for Kaplan-Meier and Cox proportional hazards analyses of dementia progression, severe disability, institutionalization, and mortality has been completed.

3. Submission of an abstract to American Academy of Neurology and potentially a second one to Alzheimer’s Association International Conference.
Although the original proposal anticipated submission of an abstract to the American Academy of Neurology (AAN) and potentially the Alzheimer's Association International Conference (AAIC), the investigative team elected to prioritize completion of dataset refinement and methodological development before disseminating results. Given the complexity of the longitudinal analyses and the opportunity to substantially strengthen the scientific rigor of the study, abstract submission was deferred until completion of the primary analyses. This decision is expected to improve the quality and impact of future scientific presentations.

4. Manuscript preparation for publication.
Manuscript development has begun through extensive refinement of the study rationale, hypotheses, outcome measures, and statistical framework. The study has evolved from a relatively straightforward observational comparison into a more rigorous longitudinal investigation designed to address important methodological limitations present in prior studies of ChEI use during prodromal Alzheimer's disease. Completion of the primary analyses is expected to support manuscript submission during the upcoming project period.

5. Long-term outcome, if supported by the results, would include preliminary results to support a Ph4 pragmatic trial grant application.
The project has established a robust methodological framework for evaluating symptomatic therapies in biologically confirmed Alzheimer's disease by leveraging autopsy-confirmed AD neuropathology, thereby addressing an important limitation of prior studies that relied solely on clinical diagnoses and included heterogeneous underlying pathologies. The resulting dataset provides a strong foundation for future investigations of treatment response during the prodromal stages of Alzheimer's disease and may support additional studies incorporating biomarker-defined populations as these datasets continue to expand. Completion of the planned analyses

is expected to generate preliminary evidence for future external funding applications focused on optimizing symptomatic treatment strategies in early Alzheimer's disease, particularly in the era of easily accessible biomarker testing. During the upcoming project period, the investigative team plans to complete the primary statistical analyses, submit the findings for presentation at national scientific meetings, including the American Academy of Neurology and the Alzheimer's Association International Conference, and prepare a peer-reviewed manuscript describing the longitudinal cognitive, functional, neuropsychiatric, and survival outcomes associated with ChEI exposure in autopsy-confirmed Alzheimer's disease.

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ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Patient-based live cell banking for translational research. Geidy Serrano, PhD, Suet Theng Beh, PhD, Lalitha Madhavan, Ignazio Piras, PhD (Consultant), Thomas Beach, MD, PhD. Banner Sun Health Research Institute; University of Arizona (Tucson); Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

The goal of this project is to establish and expand a comprehensive live-cell biorepository from clinically and neuropathologically characterized Brain and Body Donation Program (BBDP) participants. The project focuses on:

1) expanding the fibroblast bank from donors with Alzheimer's disease (AD), Parkinson's disease (PD), related disorders, and cognitively normal controls;
2) evaluating fibroblasts as a translational model of mitochondrial and autophagy dysfunction in AD;
3) generating and banking induced pluripotent stem cell (iPSC) lines from selected fibroblast cultures; and
4) expanding peripheral blood mononuclear cell (PBMC) banking for future disease modeling and reprogramming studies.

Background and Significance:

The Cell Core provides renewable human cell models derived from one of the world's best-characterized longitudinal clinicopathological aging cohorts. These resources support disease modeling, biomarker discovery, organoid development, and therapeutic testing. Only a limited number of Alzheimer's Disease Research Centers routinely generate and bank fibroblasts and iPSCs from well-characterized donors, placing Arizona in a unique national position. State funding is critical because maintaining live-cell cultures requires specialized personnel, technical expertise, continuous cell maintenance, quality control, and laboratory supplies that are rarely supported by institutional funds or traditional research grants.

Proposed One-Year and Long-Term Outcomes:

During the previous funding period, we proposed processing 25–30 scalp tissue samples (approximately 3–4 cases per month over a 10-month period), based on an anticipated fibroblast generation success rate of 70% and the requirement of 2–3 months for fibroblast culture and expansion per case. We also proposed expanding the repository to include underrepresented disease groups and rare APOE genotypes. In addition, we anticipated collecting longitudinal PBMC samples from living participants, with a goal of banking at least two PBMC collections from approximately 50 individuals. Given the strong interest from the Michael J. Fox Foundation, which sponsored the purchase of a dedicated cryogenic freezer in early 2025 and promoted the availability of these samples to investigators within its funded research network, we proposed making these PBMC resources available to scientists interested in generating iPSCs from PBMCs as an alternative to fibroblast-based reprogramming. Furthermore, we proposed continuing the generation of fibroblast-derived iPSC lines and initiating PBMC-derived iPSC production, completing validation studies of disease-related cellular mechanisms in patient-derived fibroblasts, distributing cell resources to investigators, publishing technical and scientific manuscripts, and expanding collaborative research projects. Our long-term goal was to establish Arizona as a premier resource for renewable patient-derived cell models that support investigator-initiated research, industry partnerships, biomarker discovery, mechanistic studies of neurodegenerative disease, and therapeutic development.

Year-End Progress Summary

The Arizona Alzheimer's Consortium Cell Core continued to expand one of the nation's few comprehensive live-cell biorepositories for neurodegenerative disease research. State funding provided the critical personnel effort and laboratory supplies required to establish, expand, quality control, cryopreserve, and distribute patient-derived fibroblasts, PBMCs, and induced pluripotent stem cells (iPSCs). These activities are highly specialized, labor intensive, and require continuous cell culture maintenance, including work during weekends and holidays. Because this type of infrastructure is rarely supported by institutional funds or traditional research grants, continued state investment is essential to sustain this unique resource.

During this funding period, we successfully banked 30 new fibroblast lines from clinically and neuropathologically characterized donors, established PBMC banks from 53 living participants, cryopreserved approximately 586 million PBMCs across 267 vials, and generated 12 induced pluripotent stem cell (iPSC) lines (6 in-house and 6 through collaboration with Dr. Lalitha Madhavan). These efforts increased our total iPSC collection to 17 cases. We also optimized reprogramming protocols for samples from older donors and trained additional personnel, thereby expanding the long-term capacity of the Cell Core.

We maintained a fibroblast generation success rate exceeding 80%. Successfully banked cases included cognitively normal controls, Alzheimer's disease (AD), mild cognitive impairment (MCI), Parkinson's disease (PD), and one case with a pending diagnosis. The cohort banked during this reporting period included 17 female and 13 male donors, with a mean age of 88 years (range: 51–102 years). These additions expanded the repository to more than 147 cases and over 6658.77 million banked cells.

PBMCs were successfully isolated and cryopreserved from 53 clinically characterized living participants, including 34 cognitively normal controls, 17 PD cases, 1 participant who progressed from cognitively normal status to MCI, and 1 case of dementia with Lewy bodies (DLB). Approximately 586.4 million PBMCs were cryopreserved across 267 vials, including both high-density and lower-density aliquots to support a range of downstream applications. The PBMC bank represents a valuable resource for immune profiling, biomarker discovery, disease-comparison studies, and future cellular reprogramming efforts.

In addition, PBMC characterization and PBMC-to-iPSC reprogramming studies have been initiated. One PBMC reprogramming case is currently underway to evaluate the feasibility of generating iPSCs from cryopreserved PBMCs obtained from older donors. During the next funding period, we plan to bank PBMCs from approximately 50 additional participants, with emphasis on cognitively normal controls, MCI, AD, and PD cases. We will also continue the development and optimization of PBMC-to-iPSC reprogramming protocols and further characterize banked PBMC samples to enhance their utility for future research studies.

Our Cell Core has become an important shared resource for investigators in Arizona and beyond. Researchers now routinely request our fibroblasts for disease modeling and reprogramming into iPSCs, and multiple investigators are incorporating our Cell Core into grant applications to generate patient-derived cell models. These renewable human cell resources support biomarker discovery, mechanistic studies, organoid development, drug screening, and therapeutic research.

In addition to expanding the repository, we demonstrated that patient-derived fibroblasts retain disease-relevant biological alterations, including mitochondrial dysfunction and impaired autophagy associated with Alzheimer's disease (AD). As the first phase of Aim 2, RT-qPCR analysis was completed using passage 15 fibroblasts from 5 cognitively normal control cases and

5 AD cases. Compared with controls, AD fibroblasts exhibited reduced expression of genes involved in mitochondrial fusion, including mitofusin 1 (MFN1), mitofusin 2 (MFN2), and optic atrophy 1 (OPA1), along with increased expression of mitochondrial fission-associated genes, including dynamin-related protein 1 (DRP1) and mitochondrial fission factor (MFF). In addition, AD fibroblasts demonstrated elevated p62 expression and reduced microtubule-associated protein 1 light chain 3 (LC3) expression, findings consistent with impaired autophagic flux and decreased cellular clearance mechanisms. These results indicate that fibroblasts preserve key disease-associated cellular phenotypes and support their use as an accessible, cost-effective translational model for investigating cellular senescence, mitochondrial dysfunction, and neurodegenerative disease mechanisms. Collectively, these findings extend the scientific value of the Cell Core repository beyond iPSC generation and provide a platform for mechanistic studies and therapeutic screening in age-related neurodegenerative diseases.

This investment has positioned Arizona as a national leader in patient-derived live-cell banking. Only a limited number of Alzheimer's Disease Research Centers routinely generate and bank fibroblasts and iPSCs from deeply characterized donors, making this Core a unique resource for the scientific community. The Cell Core now supports local, national, and international collaborations and continues to attract new investigators, collaborative projects, and external funding opportunities. Continued state support will ensure the expansion of these high-value resources, increase scientific productivity, strengthen Arizona's research infrastructure, and accelerate the development of new therapies for Alzheimer's disease and related neurodegenerative disorders.

BARROW NEUROLOGICAL INSTITUTE
PROJECT PROGRESS REPORTS

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Investigating Autonomic Dysfunction in Alzheimer's Disease Using Brain-Heart Network Connectivity. T. Noah Hutson, PhD, Susan Criswell, MD, Anna Burke, MD, Daniel Eagan, MD.
Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Specific Aims:

Hypothesis: Autonomic dysfunction severity (elevated baroreflex sensitivity, increased supine hypertension, more autonomic disruption on the COMPASS 31 questionnaire) in Alzheimer's Disease (AD) is characterized by temporal network instability of electrophysiological brain-heart communication (EEG-ECG). The impaired communication between the brain and heart will also be reflected in unstable spatial network activity in the brain (fMRI). We propose that these abnormalities are driven by neurodegenerative network interruptions, with specific, identifiable brain regions within the Central Autonomic Network (CAN) contributing to autonomic dysfunction representing therapeutic targets for the autonomic symptoms of AD.

Specific Aim 1: Compare temporally resolved brain-heart network stability from EEG-ECG recordings in 15 AD patients with minimal or no autonomic dysfunction symptoms (MD) [COMPASS 31 score <=15, no OH] and 15 AD patients with significant autonomic dysfunction (SD) [COMPASS 31 score > 15 and/or OH] via binary generalized linear models (GLM).
Specific Aim 2: Evaluate spatially resolved network stability of brain-heart communication from fMRI as a marker of autonomic dysfunction in AD. We will compare spatial stability of the CAN between our MD and SD groups via binary GLM analyses.

Background and Significance:

Alzheimer's Disease (AD) is a neurodegenerative condition estimated to affect nearly 7 million Americans over 65 years in age. In AD, progressive neurodegeneration leads to cognitive decline and behavioral abnormalities. Autonomic dysfunction is a common comorbidity of AD with an increasing prevalence as the disease advances, resulting in urinary, gastrointestinal, sexual, and cardiovascular dysfunction including orthostatic hypotension (OH). Cardiovascular autonomic dysfunction is a significant complication with limited treatment options for patients with AD, representing increased injury risk from falls. Despite the frequency and severity of these symptoms, our understanding of the underlying mechanisms of autonomic dysfunction in AD severity remains extremely limited.

Autonomic homeostasis is maintained by the brain's network of complex and highly efficient communication hubs, with relay inputs from within and external to the central nervous system. Cardiac input to the brain from various chains of communication (electrophysiological, neurochemical and metabolic) creates a robust control scheme under healthy conditions, but this communication is impaired in neurodegenerative diseases like AD.

Brain regions affected by AD exhibit overlap with components of the central autonomic network (CAN), posing a threat to CAN stability. Functional connectivity in the CAN has been linked to AD biomarkers via combined fMRI-plasma analysis, but this has not been associated directly with autonomic dysfunction in AD. Further, current examination of brain and cardiac networks in AD using electroencephalography (EEG) and electrocardiography (ECG) evaluate these networks separately. However, these organs do not exist in isolation and while such approaches may quantify cardiac and neurologic contributions to autonomic dysfunction, they fail to capture directed interactions between the two. As a result, much remains unknown about the regional innerworkings of these brain-heart relationships and the subsequent development of autonomic dysfunction in AD. Integration of cardiac signals into EEG networks will allow for an innovative multi-organ approach to understanding AD-associated autonomic dysfunction.

Network analysis of brain-heart interactions on temporally (EEG-ECG) and spatially (fMRI) resolved scales coupled with cognitive, autonomic, motor and demographic phenotyping will allow us to evaluate the integrity of communication between these systems and identify region-specific behaviors associated with autonomic dysfunction in AD. Identification of regional and relational mechanisms of AD-associated autonomic dysfunction will lay the foundation for improving the treatment of autonomic dysfunction in AD.

Preliminary Data, Experimental Design and Methods:

Participant Recruitment: All 30 participants will be recruited from the Barrow Neurological Institute.

Screening Phase: Subjects will be screened initially via phone call and remote COMPASS 31 exam. The COMPASS 31 exam is a 31-question self-administered evaluation of autonomic symptoms and has been abbreviated from its predecessors for simplicity and robust estimation of symptom burden[29]. Subjects matching initial screening criteria will be brought in for final in-person screening to formally evaluate for OH and COMPASS 31 validation prior to scheduling electrophysiology and neuroimaging.

Evaluation Phase: Participants will be evaluated by a board-certified Neurologist for AD diagnosis. Participants will complete the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) cognitive battery. Participants will then be scheduled for non-contrast MRI (1-hour) and EEG-ECG recordings (20 minutes).

AIM1: Electrophysiology and Brain-Heart Dynamics: Each subject will undergo a 20-minute resting state EEG-ECG recording on the currently deployed EEG devices at BNI.

Brain-Heart Network Analysis: We will employ GPDC to estimate network connections between the heart (ECG) and all available EEG contacts. Using surrogate analysis to filter connectivity values, we will estimate a single value of temporal network stability per electrode/subject.

Aim 1 Outcome Variables: EEG-ECG network **temporal stability** (per EEG electrode).

AIM 2: Functional Neuroimaging and Metabolic Networks: We will compare CAN stability of FC between the SD and MD groups using rs-fMRI. We will collect standard ADNI protocol T1, T2, and DTI. We will perform exploratory analysis on white matter tracts via diffusion tensor imaging (DTI) and corroborate abnormal network activity with fractional anisometry (FA), a measure of white matter tract integrity[36].

Aim 2 Outcome Variables: fMRI network **spatial stability** (estimated across all voxels within CAN VOIs) for all participants.

Proposed One-Year and Long-Term Outcomes:

One-Year Outcomes:

- Collect neuroimaging, electrophysiology, medical history, cognitive battery and autonomic function data in 30 participants with AD
- Pre-process functional imaging data using complex multi-echo pipelines
- Pre-process EEG-ECG data to clean artifacts
- Statistically analyze imaging and electrophysiology data to evaluate relationships between autonomic function and brain networks
- Prepare findings for publication

Long-term outcomes:

- Leverage data for external funding application (R01) investigating brain-hear-network mechanisms of autonomic dysfunction.
- Identify specific brain regions and networks contributing to autonomic dysfunction and ultimately identify therapeutic targets for autonomic symptoms of AD.

Year End Progress Summary:

For this project, we are seeking to investigate brain networks involved in autonomic dysfunction in Alzheimer's Disease through clinical evaluations, fMRI and EEG. Over the last 10 months we have made great strides towards this goal. Upon receiving the award letter, we worked to obtain IRB approval and receive institutional approval via a DHARE "Go Letter". Additionally, we worked to streamline participant recruitment, scheduling practices and sample banking. We also designed and implemented cognitive batteries to be collected with Dr. Eagan and Jessica Bez-Cruz. We received IRB approval for the study and began recruiting subjects according to our planned strategy. To date, 11 participants have completed enrollment, 5 are scheduled to complete the study within the month (May), and an additional 4 patients are in the scheduling process.

In parallel, we worked to develop pipelines for transfer of MRI and EEG data from clinical settings to our research server. This included assisting with implementation of an institution-wide imaging transfer system (Xnat) supported by multiple projects. Once initial studies were transferred to our research environment, we began to develop and refine pre-processing techniques for the MRI and EEG data. After pipelines were finalized for data, we performed data cleaning and preliminary feature estimates on all imaging data collected in the course of the study.

We developed novel measures of brain-heart network stability to be estimated from fMRI and EEG-ECG data leveraging established mathematical principles, which can be applied to all imaging/electrophysiology data collected in the course of the study. We have begun analyzing the data collected to date with the new analytical frame work, and will be able to report key findings by the project's end, once all data has been collected and compiled.

Thus far, the data shows a broad span of Compass-31 values (from 0 to >50), representing a wide range of autonomic dysfunction, which will allow us to thoroughly investigate the relationship between functional networks and autonomic dysfunction in high spatial and temporal resolution. Image and EEG quality for all participants in the study has been excellent, with no participant records failing current quality control checks.

We have also banked blood-plasma samples to evaluate AD biomarkers in the context of the brain networks we are investigating as well as the measures of autonomic dysfunction. These results will be produced once all data is collected for the course of the study, as the panel analysis is done in batch format. The cognitive performance data collected will also be used in exploratory analysis, evaluating how brain-heart connections relate to cognition and blood-biomarkers. The collection of additional MRI sequences (other than fMRI) will allow us to investigate other structural and functional properties of the brain in the context of AD related autonomic dysfunction. Thus, this project has provided a rich dataset for exploration and further analysis adding onto the initial primary outcomes.

Once preliminary results for our outcome are complete, we will work to prepare an abstract, publication, and application for external funding to build upon the work completed in the course of this project.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Traffic Related Air Pollution and Tree Density on Risk of Alzheimer's Disease. Jordan Killion, PhD, MPH, Brittany Krzyzanowski, PhD, Sai Shivani Chirag, MA. Barrow Neurological Institute; Atria and University of Minnesota; Arizona Alzheimer's Consortium.

Specific Aims:

Aim 1: We will test for both a county-level and neighborhood-level interaction between traffic related air pollution (TRAP) emissions and deciduous tree density on the risk of Alzheimer's disease (AD). Specifically, we will use data on on-road air pollution in the form of particulate matter <2.5 microns in diameter ($PM_{2.5}$), nitrogen oxides (NOx), and volatile organic compounds (VOCs) for the year 2017 from Neighborhood Emission Mapping Operation (NEMO), average annual daily traffic (AADT) for the years 1997-2010 from ESRI, and deciduous tree density from the USDA to compute both county- and block group-level average TRAP emissions and tree density for use in a case-control study of AD risk. This study will leverage a population-based Medicare dataset of 221,843 incident AD patients and 20,032,717 population-based controls.

Aim 2: To assess regional variation of biogenic-anthropogenic mixing across the nation, we will use geographic weighted regression and county-level estimates generated from Aim 1 to map the interaction coefficients and identify subregion(s) for higher resolution analysis. We will use GWR to run four models based on county-level on-road $PM_{2.5}$, NOx, VOCs, and AADT to identify regions where the interaction between TRAP and deciduous trees has the strongest effect on county-level AD risk (adjusted for age, sex, race, and cardiometabolic diseases).

Aim 3: To explore how different sources of TRAP and different tree types interact to effect risk of AD, we will use higher-resolution (1 to 22 km2) estimates of on-road $PM_{2.5}$, NOx, VOCs, and AADT and density of deciduous, conifer, and mixed forests within a 5-mile radius of each beneficiary's zip+4 location to test the association with AD risk in our subregion(s).

Background and Significance:

Several studies have established a link between $PM_{2.5}$ and AD. More recently, investigators identified an interaction between manmade (anthropogenic) air pollution and natural (biogenic) emissions from trees. The role of this interaction in the context of human health, and AD risk in particular, remains understudied despite growing evidence from cell and animal models. Notably, a recent mouse study found that when $PM_{2.5}$ interacts with anthropogenic VOCs it induces greater AD-related pathologies compared to PM2.5 exposure alone. These findings warrant human epidemiological studies focusing on the potential for biogenic VOCs from trees to interact with $PM_{2.5}$ to induce AD by a similar mechanism. Recent research from our laboratory identifies a much greater risk of AD in the Southeastern U.S., largely related to the greater disease burden of diabetes and cardiovascular disease. However, this region also has the greatest mixing of PM2.5 and biogenic VOCs from dense deciduous forests as well as PM2.5 generated from traffic, i.e. traffic related air pollution. Understanding the interaction between TRAP and biogenic VOCs emitted from trees offers promises to provide novel insight into environmental mechanisms leading to geospatial concentration of AD in the U.S. given that the southeast central part of the nation has the highest incidence of AD, the greatest number of VOC-emitting deciduous trees, and dense road networks. In this proposal, we will first obtain evidence of biogenic-anthropogenic mixing as a nationwide modifiable risk factor for AD by exploring the interaction between TRAP emissions and deciduous tree density on the risk of AD for both county-level and block group data. Then we will assess the regional variation of the interaction effect across the nation using geographically weighted regression to create a county-level map that will inform public health

measures to mitigate the interaction between TRAP emissions and VOCs from trees as a prevention strategy for AD. With this interaction map, we will also identify subregions for a higher-resolution person-level analysis using exposures assigned at the 1km2 level to explore how different sources of TRAP and different tree types interact to impact AD risk. This proposal will utilize advanced geographic information systems (GIS), high-resolution data on traffic emissions including on-road $PM_{2.5}$, NOx, VOCs, and satellite-derived data on the density of deciduous, conifer, and mixed forests in the 3-mile radius surrounding the zip+4 location of Medicare beneficiaries from a nationwide dataset of 500,000 incident AD patients and 22 million population-based controls. This study will identify and elucidate the public health impacts of the interaction between manmade emissions and natural emissions from trees, offering new approaches for AD prevention by guiding emissions standards for specific TRAP components in targeted regions across the nation.

Preliminary Data, Experimental Design and Methods:

We conducted a preliminary investigation into the interaction of NOx emissions and deciduous tree density on dementia risk in Tennessee and Alabama (two states with relatively high road network and deciduous tree density). Our preliminary study included 27,034 cases and 713,701 controls as well as 1km2 NOx estimates and block group level deciduous tree density. After adjusting all models for well-established risk factors of dementia (i.e., age, race, sex, prevalent cardiometabolic diseases, and educational attainment), we found a compelling trend towards an interaction effect between NOx and deciduous tree density on risk of dementia (lrtest= 0.0537) (Figure 1). These data support the need to conduct further analyses using higher resolution exposure data to explore associations with incident AD across a larger geographic region.

Proposed One-Year and Long-Term Outcomes:

This proposal offers to advance our knowledge of a modifiable risk factor (TRAP), its subcomponents, and its interaction with tree density to effect risk of AD. With the results of this study, we will be well positioned to investigate, and potentially identify, the specific sources of TRAP in the Southeast Central US (the region of the nation with the highest incidence of AD). In doing so, we should be able to provide specific guidance to direct efforts for environmental remediation in targeted regions based on specific TRAP emissions and local tree type and tree density.

Year End Progress Summary:

Accomplishments for this study have been that we have successfully conducted a nationwide, population-based, geographic study of 15 million Medicare beneficiaries aged 67 and older, including 574,477 individuals with incident dementia. We were able to obtain and process exposure data for on-road emissions of nitrogen oxides (NO_x), volatile organic compounds (VOCs), sulfur dioxide (SO_2), ammonia (NH_3), carbon monoxide (CO), particulate organic carbon (POC), particulate elemental carbon (PEC), air pollution in the form of particulate matter <2.5 microns in diameter ($PM_{2.5}$), and course particulate matter (PMC) from the Neighborhood Emission Mapping Operation (NEMO) for 2017, as well as average annual daily traffic (AADT) data from 1997–2010 (ESRI). Furthermore, we obtained data on tree type (i.e., deciduous, evergreen, wetland, etc.) and density was estimated using USDA satellite-derived land cover data.

Using these exposure variables and our Medicare dataset, we used principal component analysis (PCA) to address multicollinearity. We then successfully ran logistic regression models to quantify the effect of TRAP, tree density, and their interaction on dementia risk, adjusting for age, sex, race, cardiometabolic disease, and neighborhood level income and educational attainment. Our findings provide compelling new evidence that the interaction between anthropogenic air pollution

and natural emissions from trees contributes to elevated risk of AD in the United States. Specifically, we observed a significant positive interaction between TRAP with NO_x, $PM_{2.5}$, NH_3, CO, PEC, POC, PMC, VOCs and their linear combination (i.e., the first principal component)—and deciduous tree density on the risk of AD.

These results support the hypothesis that co-occurring exposures to manmade emissions and biogenic volatile organic compounds (BVOCs) intensify environmental neurotoxicity, consistent with emerging biological models of AD pathogenesis. In addition, our findings also add complexity to prevailing assumptions about the protective role of greenspace. While vegetation has known mental health and air quality benefits, our results suggest that in certain environmental contexts—especially where air pollution is high—vegetative emissions may contribute to harmful atmospheric reactions that exacerbate neurological risk.

Due to severe multicollinearity, the GWR model adjusted for age, sex, race, and cardiometabolic diseases to identify regions where the interaction between TRAP and BVOC-emitting trees has the strongest effect on county-level dementia risk has yet to converge in GIS. Thus, we were unable to create the interaction map at this time. Nevertheless, we did a subregion analysis to supplement our main analysis which revealed geographic variation in the relationship. We are working to overcome the multicollinearity problem in GWR by removing or combining highly correlated predictors based on correlation and VIF, or by transforming them using PCA to create independent variables. Additionally, we will improve local model stability by limiting the number of predictors and increasing the bandwidth so that each local regression has sufficient variation and data.

This study is, to our knowledge, the first to demonstrate an interaction between TRAP emissions and BVOC-producing vegetation in relation to AD. Our findings align with recent experimental research in animal models, which showed that combined exposure to $PM_{2.5}$ and anthropogenic VOCs led to greater AD-related pathology compared to $PM_{2.5}$ alone. Importantly, our study extends these insights to human populations using high-resolution environmental exposure data and a large, population-based sample of Medicare beneficiaries. Once we get the GWR model to converge, we plan to submit manuscripts for publications.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Exploring RNA m6A Modifications: Pathways and Impacts in Dementias. David Medina, PhD, Ashley Boehringer, PhD. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Specific Aims:

Aim 1: Determine the role of m6A methylation in iPSC-based models of neurodegeneration and determine the downstream effects of m6A methylation on disease pathobiology.

Aim 2: Generate m6A epitranscriptomic profiles from AD and FTD cortical regions compared to control cases using direct RNA sequencing to identify differentially m6A-modified RNAs and affected pathways.

Background and Significance:

Neurodegenerative diseases such as Alzheimer's disease (AD), Frontotemporal Dementia (FTD), and Amyotrophic Lateral Sclerosis (ALS) remain major challenges due to limited therapeutic options and an incomplete understanding of disease mechanisms. Emerging evidence suggests that N6-methyladenosine (m6A) RNA modification plays a critical role in neuronal function and is dysregulated in these disorders. However, the mechanisms linking m6A dysregulation to neurodegeneration remain poorly understood.

m6A is the most common post-transcriptional modification of eukaryotic RNA and regulates RNA splicing, stability, translation, and overall RNA metabolism. This process is dynamically controlled by "writer," "reader," and "eraser" proteins including METTL3, METTL14, YTHDF family proteins, FTO, and ALKBH5. Recent studies have demonstrated altered m6A levels in AD, FTD, and ALS patient tissues and experimental models, suggesting that disruption of RNA homeostasis contributes to disease progression.

Our interest in this pathway was driven by findings from novel Matrin 3 S85C knock-in mouse models, which exhibit motor impairments, neuronal loss, neuroinflammation, transcriptomic alterations, and reduced m6A levels in vulnerable brain regions. Additional studies demonstrated that Matrin 3 knockdown reduces global m6A levels in neuronal cells, suggesting that Matrin 3 may regulate m6A biology. Importantly, both our group and others have identified Matrin 3 pathology in sporadic ALS, FTD, and AD tissues.

This proposal seeks to define how m6A dysregulation contributes to neurodegeneration through multidisciplinary approaches integrating iPSC-derived cortical neurons, biochemical assays, and direct RNA sequencing of postmortem brain tissue. These studies will identify disease-associated pathways, biomarkers, and therapeutic targets relevant to dementia and related neurodegenerative disorders.

Preliminary Data, Experimental Design and Methods:

We have generated preliminary data demonstrating reduced m6A levels in disease-relevant models of neurodegeneration. In Matrin 3 S85C knock-in mice, decreased m6A immunoreactivity was observed in the cerebellum in regions exhibiting neuronal degeneration. In addition, knockdown of Matrin 3 in NSC-34 motor neuron-like cells reduced global m6A levels, supporting a functional relationship between Matrin 3 and m6A regulation.

Aim 1 will utilize induced pluripotent stem cell (iPSC)-derived cortical neurons carrying disease-relevant mutations in MAPT, APP, and MATR3. Using these models, we will quantify global m6A levels, assess m6A pathway proteins by western blot, and evaluate disease-associated pathology including tau phosphorylation, amyloid solubility, and Matrin 3 protein levels. We will further

manipulate the m6A pathway through knockdown and overexpression of METTL3 to determine how altered m6A homeostasis influences neurodegenerative phenotypes.

Aim 2 will generate epitranscriptomic profiles from postmortem frontal cortex tissue from control, AD, and FTD cases using Oxford Nanopore direct RNA sequencing. This approach preserves native RNA modifications and allows identification of transcript-specific m6A alterations at single-nucleotide resolution. Sequencing and bioinformatic analyses will identify differentially modified RNAs and pathways associated with disease.

The project represents a collaboration between Barrow Neurological Institute, Arizona State University, and TGen, integrating expertise in neurodegeneration, iPSC biology, sequencing technologies, and bioinformatics.

Proposed One-Year and Long-Term Outcomes:

Completion of this project will provide foundational insight into how m6A RNA modification contributes to neurodegenerative disease mechanisms in AD and FTD. Over the next year, we anticipate identifying disease-associated alterations in m6A pathway proteins and generating epitranscriptomic datasets that reveal pathways linked to neuronal dysfunction and degeneration.

Long term, these studies will support development of new therapeutic strategies targeting RNA modification pathways and identify candidate biomarkers for neurodegenerative disease progression. The data generated from this work will also provide critical preliminary data for future NIH, DOD, and foundation grant applications focused on m6A biology and dementia therapeutics.

Year End Progress Summary:

This project established the experimental and collaborative framework necessary to investigate the role of m6A RNA modifications in neurodegeneration. We refined workflows for measuring global m6A levels in neuronal systems and integrated approaches for evaluating disease-associated pathological features including tau phosphorylation, amyloid solubility, and Matrin 3 biology.

We have completed sequencing of 24 postmortem tissue samples, including tissues from control patients as well as patients with FTD and AD. In addition, we incorporated ALS spinal cord tissue samples to further elucidate m6A-associated pathways across neurodegenerative diseases. The sequencing datasets are currently in the final stages of primary bioinformatic analysis. These data will allow us to identify dysregulated pathways and specific genes of interest for downstream validation studies, biomarker development, and potential therapeutic targeting.

In parallel, iPSC-based cellular models have been successfully generated from AD- and FTD-associated lines. This work included the integration of neuronal reprogramming and differentiation approaches to establish a platform for the proposed mechanistic studies and future investigations. These cells are currently undergoing differentiation and characterization for disease-associated pathological phenotypes. The work completed during this reporting period has positioned the project for large-scale mechanistic studies and future therapeutic development efforts focused on RNA modification pathways in neurodegenerative disease.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Revealing the secrets of the Mitochondria in the default mode network in Superagers.

Sylvia E. Perez, PhD. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Specific Aims:

Aim 1: We hypothesize that frontal cortex (FC) and inferior temporal cortex (ITC) layer V-VI pyramidal neurons will display a greater number of mitochondria and mitochondrial respiration activity in Superagers (SA) compared to age-matched healthy controls (AHC) and mild-cognitive impairment (MCI) subjects using immunohistochemistry, immunoblot, densitometry and respirometry techniques. Data will be correlated with demographic, cognitive performance, and neuropathological criteria.

Aim 2: We hypothesize that the two default mode network (DMN) hubs, FC and ITC, will display comparable upregulation of classes of genes related to mitochondrial function (oxidative phosphorylation), cell survival and metabolism and downregulation of oxidative stress transcripts in SA, that will be greater than AHC and MCI. We will use qPCR to validate differentially regulated genes.

Background and Significance:

Normal aging is typically associated with cognitive decline; however, a unique population of adults over 80 years of age, termed SA, maintain episodic memory performance comparable to individuals 20-30 years younger. Neuroimaging studies demonstrate that SA exhibit preserved structure and function within key regions of the DMN, including the anterior cingulate and prefrontal cortices, with larger cortical volumes and stronger functional connectivity compared to AHC. These features correlate with superior episodic memory performance. Neuropathological studies further indicate that SA generally display low tau pathology and preserved neuronal integrity despite amyloid burdens comparable to age-matched controls, suggesting enhanced neuronal resilience rather than absence of pathology. Together, these findings support the concept that DMN neurons in SA possess intrinsic protective mechanisms that preserve cognition during aging.

This application is innovative because it investigates mitochondrial function as a key mechanism underlying neuronal resilience and preserved memory in SA, an area that remains largely unexplored. The study integrates advanced human tissue-based approaches, including mitochondrial immunohistochemistry with densitometry, Seahorse respirometry on frozen-thawed brain tissue, and RNA transcriptomics coupled with functional pathway enrichment analyses to assess mitochondrial bioenergetics and function in SA neurons. By linking mitochondrial integrity to cognitive preservation, this work may identify novel mitochondrial biogenesis and metabolic pathways as therapeutic targets to maintain or improve cognitive function during aging and early Alzheimer's disease. These studies provide critical translational insight into mechanisms of successful cognitive aging and may guide future transcription-based therapeutic strategies for age-related neurodegenerative disorders.

Preliminary Data, Experimental Design and Methods:

Our preliminary studies identify mitochondrial function as a potential mechanism underlying neuronal resilience in SA. RNA sequencing revealed significant upregulation of mitochondrial ATP synthase genes (MT-ATP6, MT-ATP8, ATP5F1A, ATP5PF) and electron transport chain-related genes (COX17, UQCRFS1) in FC and ITC neurons of SA compared to AHC. Immunohistochemical analyses further demonstrated increased mitochondrial abundance and higher mitochondrial labeling density in pyramidal neurons and neuropil of SA brains. Importantly, mitochondrial transcript levels and mitochondrial density strongly correlated with cognitive

performance and episodic memory scores. Despite similar β-amyloid plaque levels between SA and controls, SA neurons exhibited enhanced mitochondrial content in the absence of tau pathology, supporting the hypothesis that increased mitochondrial bioenergetic capacity contributes to neuronal resilience. Since mitochondria are essential for ATP production, oxidative stress regulation, calcium homeostasis, and synaptic function, these findings suggest that preserved mitochondrial function may provide the energetic reserve necessary to maintain neuronal integrity and memory function during aging.

The overall premise of this project is that enhanced mitochondrial function in pyramidal neurons within DMN hubs, specifically the FC and inferior temporal cortex ITC, promotes neuronal resilience and preserves memory function in SA. This study will be the first to directly investigate the contribution of mitochondria to cognitive resilience in SA compared to AHC and individuals with MCI. Well-characterized postmortem brain tissue from SA, AHC, and MCI participants obtained through the Rush Religious Orders Study will be analyzed using rigorous, blinded experimental and statistical approaches.

Specific Aim 1 will determine whether SA exhibit increased mitochondrial abundance and respiratory function in FC and ITC pyramidal neurons. Immunohistochemistry, densitometry, and quantitative immunoblotting will be used to quantify mitochondrial proteins and distribution in cortical tissue. In parallel, seahorse-based respirometry optimized for frozen-thawed human brain tissue will assess mitochondrial respiratory capacity and oxygen consumption as measures of oxidative phosphorylation and ATP-generating function. We hypothesize that SA will display greater mitochondrial density and higher respiratory capacity compared to AHC and MCI, reflecting enhanced neuronal bioenergetic resilience.

Expected Outcomes and Interpretations: We predict higher numbers of mitochondria proteins in the FC and ITC in SA followed by AHC and MCI, reflecting greater neuronal resilience conferred by the mitochondria in SA. ***Alternatively***, we may find that western blots reveal no differences in mitochondria levels compared to that seen in individual neurons in the FC or ITC in SA compared to AHC and MCI, since immunoblotting uses tissue homogenates containing numerous cell types in addition to pyramidal neurons. ***Expected Outcomes and Interpretations:*** Since SA displayed more mitochondria in pyramidal neurons, we expect larger respiratory capacity in this group compared to AHC and MCI groups, in both hubs, FC and ITC. However, we do not rule that neither hub in SA exhibited larger OCR compared to NCI and MCI cases, as this procedure is performed in tissue homogenates containing different cellular types.

Specific Aim 2 will define the molecular signature associated with mitochondrial resilience in SA using RNA transcriptomic profiling of FC and ITC tissue. RNA sequencing and functional pathway enrichment analyses will identify differentially expressed genes related to mitochondrial biogenesis, oxidative phosphorylation, metabolism, cell signaling, cell survival, and oxidative stress pathways. We expect SA to demonstrate upregulation of genes supporting mitochondrial function and cellular resilience compared to AHC and MCI. Together, these studies will provide novel mechanistic insight into how mitochondrial bioenergetics contribute to preserved cognition and successful brain aging. ***Expected Outcomes and Interpretations:*** We provide novel insight into the molecular signature of FC and ITC in SA, which is lacking in the field. We expect a greater upregulation of transcript associated with mitochondria metabolism (biogenesis/mitophagy, fission/fusion and oxidative phosphorylation), cell metabolism and cell survival compared to AHC and MCI, since pyramidal neurons in SA display a great number of mitochondria. ***Alternatively:*** The expression of only mitochondrial function related genes will be up-regulated in SA.

Proposed One-Year and Long-Term Outcomes:

We expect that all experimental work proposed here will be finalized and data collected by the end of this proposal.

Year End Progress Summary:

Aim1: Immunoblotting, Immunohistochemistry and respirometry

FC immunoblotting and immunohistochemistry data were analyzed (see below), whereas experiments in the ITC are still ongoing. These findings revealed that several proteins associated with mitochondrial metabolism, mitochondrial biogenesis, mitophagy, small heat shock proteins, synaptic plasticity/signaling, and cellular metabolism were significantly upregulated in the FC of SA cases. These results suggest that the FC in SA individuals operates at a higher metabolic and energetic state and may be better equipped to resist age-related cellular and molecular stressors compared to AHC cases.

Immunoblotting

Small heat shock proteins: Several small heat shock proteins (HSPBs) associated with cellular stress protection and mitochondrial maintenance were significantly elevated in the FC of SA cases compared with AHC. Specifically, HSPB2, HSPB3, HSPB6, and HSPB8 were increased, whereas HSPB1, HSPB5, and HSPB7 were unchanged. No differences were observed between resilient and resistant subgroups in both SA and AHC. **Mitochondrial biogenesis:** Proteins involved in mitochondrial biogenesis and metabolic regulation, including NRF1, NRF2, and Sirtuin1, were significantly upregulated in SA compared with AHC, suggesting enhanced mitochondrial adaptive responses. In contrast, PGC-1α and TFAM levels were unchanged. No subgroup differences were detected. **Mitophagy:** BNIP3L/NIX, a receptor involved in ubiquitin-independent mitophagy was significantly increased in SA, while FUNDC1 and DRP1 remained unchanged. Within SA, resistant cases exhibited higher BNIP3L/NIX levels than resilient cases. **Mitochondria-Endoplasmic reticulum (ER) associated proteins:** Proteins involved in mitochondria-associated membrane (MAM) signaling, specifically MFN2 and GRP75, were significantly elevated in SA. Although overall BAP31, VDAC1, and PTPIP51 levels were unchanged between groups, resilient SA cases showed significantly higher levels of all MAM-related proteins compared with resistant SA cases, suggesting enhanced mitochondria-ER connectivity in resilient individuals. **Cellular metabolism:** LDHA and LDHB protein levels were significantly elevated in SA compared with AHC, indicating greater metabolic activity. **Synaptic plasticity and signaling:** TCIM and total ERK1/2 protein levels were significantly increased in SA, whereas phosphorylated ERK1/2, the p-ERK1/2: ERK1/2 ratio, and β-catenin levels were unchanged. No resilient-versus-resistant differences were observed. **Mitochondrial electron Transport Chain Proteins:** *The analysis is still ongoing*.

Immunochemistry and densitometry

Densitometry analysis revealed higher levels of the translocase of the outer mitochondrial membraneTOM20 and cytochrome c in FC layer V-VI projection neurons in SA compared with AHC suggesting an enhanced mitochondrial integrity and oxidative metabolic capacity in these neurons. TOM20 is a mitochondrial import receptor associated with mitochondrial mass and mitochondrial health. Increased TOM20 levels may indicate greater mitochondrial content, improve mitochondrial maintenance, or enhance mitochondrial protein import capacity. Cytochrome c is a key component of the mitochondrial electron transport chain involved in oxidative phosphorylation and ATP production. Higher cytochrome c levels suggest increased respiratory activity and energy production capacity, which may support the high synaptic and metabolic demands of large projection neurons in cortical layers V-VI. Because layer V-VI pyramidal neurons are highly metabolically demanding and vulnerable to aging and neurodegeneration, preservation of mitochondrial function in these neurons could contribute to the exceptional cognitive performance observed in SA.

Together, these preliminary findings in the FC suggest that SA maintain better mitochondrial function and bioenergetic efficiency, greater resistance to age-related mitochondrial dysfunction, enhanced neuronal resilience and survival, and preserved synaptic activity and long cortical connectivity that translated into an exceptional episodic memory.

Seahorse-based respirometry
Frozen FC and ITC tissues were sent to our collaborators at University of California, Los Angeles to assess mitochondrial respiratory capacity and oxygen consumption as measures of oxidative phosphorylation and ATP-generating function in SA and AHC. Results are pending.

Specific Aim 2
RNA transcriptomic profiling of FC and ITC tissue will be used to define the molecular signatures associated with mitochondrial resilience in SA. RNA has been successfully extracted from FC and ITC samples, and RNA sequencing will be performed by our core facility in June. Preliminary results are anticipated by early July.

Future Studies*:* Some of the data obtained in this proposal is part of recently published work (**see below**), and we expect to publish all findings generated by this proposal by the end of the year. I also plan to apply for federal funding (NIH R01 or R21) and private foundation support (Alzheimer's Association).

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Acute Effects of Exercise, With and Without Anti-Amyloid Therapy, on Fluid Biomarkers in Patients with Mild Cognitive Impairment Due to Alzheimer's Disease. Marwan N. Sabbagh, MD, FAAN, FANA, Susan B. Racette, PhD, FTOS. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.

Specific Aims:

- **Aim 1.** Evaluate the acute effects of aerobic exercise, independently and when combined with anti-amyloid therapy (AAT), on physiological pathways that impact amyloid-beta (Ab) deposition and neurogenesis in patients with mild cognitive impairment (MCI) or mild dementia.
- **Aim 2.** Explore the time course of fluid biomarker concentrations for 48 hours following acute exercise in patients with MCI or mild dementia, with and without anti-amyloid therapy.

Background and Significance:

Alzheimer disease (AD) is the most prevalent neurodegenerative disorder, affecting an estimated 7.4 million Americans and more than 55 million people worldwide. AD is characterized by cognitive impairment and functional decline, which have dramatic adverse effects on social function, physical function, quality of life, and productivity. AD also is a major cause of death. Pathological changes in AD include Aβ protein aggregation and plaque formation between neurons and tau protein tangles within neurons. MCI represents the earliest clinical diagnosis of cognitive decline and a potential window of opportunity during which interventions may interrupt or slow disease progression by impacting inflammation, excitotoxicity, neurochemical breakdown, autophagy, and other relevant pathways. Monoclonal antibodies are promising pharmacologic anti-amyloid treatments that reduce Aβ plaques in the brain and have modest benefits in slowing cognitive decline. Two currently available, FDA-approved AATs are lecanemab (LEQEMBI®, approved July 6, 2023) and donanemab (Kisunla®, approved July 2, 2024). Careful patient selection is important to minimize the risk of amyloid-related imaging abnormalities (ARIA). There is compelling evidence that aerobic exercise stimulates neurogenesis, reduces neuroinflammation, reduce Aβ plaques in AD animal models, and slows cognitive decline.

Experimental Design and Methods:

- *Design & Eligibility Criteria:* This is a cross-sectional study to evaluate the metabolic responses to a single exercise bout in patients with MCI or mild dementia who are receiving or not receiving AAT. Eligible patients are men and women aged 60-90 years who have MCI or mild dementia and amyloid positivity based on cerebrospinal fluid Aβ analysis or positron emission tomography imaging. Group 1 patients have been on AAT for at least 6 months at the time of study enrollment; Group 2 patients are not receiving AAT. Patients are recruited from the Barrow Neurological Institute (BNI) Alzheimer's & Memory Disorders Program.
- *Screening:* Pre-screening is completed during a clinic visit or by phone. Individuals who meet the criteria to proceed are invited to complete a screening visit at BNI, which includes Capacity to Consent, written informed consent, Physical Activity Readiness Questionnaire (PARQ), Montreal Cognitive Assessment (MoCA), six-minute walk test, and medical history / medications.
- *Study Visits:* Eligible individuals complete 3 study visits at the Arizona State University (ASU) Translational Research Center in the 850 PBC building on the ASU downtown Phoenix campus. Visit 1 involves a 30-minute aerobic exercise bout at submaximal intensity (60-75% of age-predicted maximal heart rate), preceded by measurement of vitals, anthropometrics, Short Physical Performance Battery (SSPB), cognitive assessments, and questionnaires. Blood is

drawn before exercise, upon completion of exercise, 1 hour after completion of exercise, 24 hours after the exercise bout (study visit 2), and 48 hours after the exercise bout (study visit 3).

- *Biomarker Outcomes:* The major outcomes are biomarkers in plasma or serum that are relevant to amyloidogenic pathways, systemic inflammation, neuroinflammation, neurogenesis, and energy status. The neurotrophins BDNF and beta nerve growth factor (b-NGF), and the inflammatory cytokines interleukin (IL)-1b, IL-6, IL-8, IL-10, leptin, monocyte chemoattractant protein-1 (MCP-1), and tumor necrosis factor alpha (TNF-a) are quantified in serum by enzyme-linked immunosorbent assay (ELISA) with a commercial kit (MSD U-PLEX Adipokine Combo 1 [human]). Irisin, PGC-1a, sAPPα, and VEGF and the ketone body b-hydroxybutyrate are measured in serum by ELISA. b-secretase activity is measured in serum by fluorescence. Cathepsin B is measured in plasma by ELISA using a single molecule array platform. Glucose and lactate are measured in plasma using the hexokinase and lactate oxidase enzymatic methods, respectively.
- *Additional Outcomes:* A series of questionnaires and measurements are performed to characterize patients' medical, cognitive, and physical function status. Cognitive measures include FAST, MoCA, Test of Premorbid Functioning (TOPF), and Cognitive Function Instrument (CFI). Processing Speed is assessed with the Trail Making Test Part A (Trails A), Executive Function with Trails B, Quality of Life with the WHOQOL-BREF, and Physical Function with the Short Physical Performance Battery (SPPB). Physical Activity is assessed using the Physical Activity and Sedentary Behavior Questionnaire. Dietary Patterns are estimated with the Mediterranean Eating Pattern for Americans (MEPA) instrument and Sleep Quality with the Pittsburgh Sleep Quality Index (PSQI). Body Mass Index (BMI) is computed from measured weight (digital scale) and height (stadiometer) to determine weight status.

Proposed One-Year and Long-Term Outcomes:

- *Proposed one-year outcomes:* This project will provide novel and important preliminary data on metabolic pathways that are responsive to aerobic exercise in patients receiving AAT and whether these responses differ from those in patients not receiving AAT.
- *Proposed long-term outcomes:* The results will inform and power a longitudinal exercise intervention trial for patients receiving AAT. External funding will be sought from the NIH or other funding agencies. The long-term goal is to provide evidence-based lifestyle strategies that complement and enhance pharmacologic therapy to prevent or delay cognitive decline.

Year End Progress Summary:

- *Study Set-Up and Regulatory Approval:* As preliminary steps before launching this project, we created and tested the Research Electronic Data Capture (REDCap) database, created all participant assessment forms, developed a Manual of Procedures, obtained Institutional Review Board approval from BNI / St. Joseph's Hospital and Medical Center (IRB of Record) and from Arizona State University (reliance IRB), and trained all personnel.
- *Participant Enrollment and Study Visits:* 14 participants (7 receiving AAT and 7 not receiving AAT) will have complete data on blood biomarkers, cognitive function, and physical function by the end of the project period. As of May 1, 2026, 11 participants completed the study (7 AAT, 4 non-AAT), with the remaining 3 participants scheduled for their visits at ASU in May. The mean age of enrolled participants is 76.2 years (range 64-85); 58.3% are men.
- *Blood Biomarker Analyses:* Laboratory analyses of all blood biomarkers are being performed at ASU. All equipment, supplies, assay kits, and trained personnel are in place, with analyses on schedule to be completed by mid-June 2026.
- *Data Management and Data Analyses:* Data from the screening visit and study visits are being entered into the ASU REDCap database by the Clinical Research Coordinator at BNI and by project personnel at ASU. Data from the blood biomarker analyses will be imported into REDCap

as a CSV file. De-identified data will be exported from REDCap and data analyses will be performed by a BNI statistician.

- *Challenges and Solutions:* (a) Our team faced challenges recruiting participants who met the inclusion criteria for the non-AAT group. *Solution:* We reached out to our colleagues on other BNI study teams to facilitate sharing information with a broader population of potentially eligible participants, which was successful. (b) The multi-plex kit for analyzing 14 biomarkers simultaneously has been on backorder for several months due to the BDNF antibody being unavailable. *Solution:* We worked with the company to order a multi-plex kit without BDNF and a separate BDNF assay kit so that all analyses can be completed on schedule.
- *Future Directions:* Our team will (a) present the results of this project at local, national, and international scientific conferences (e.g., AAC and AAIC); (b) prepare and submit one or more manuscripts to peer-reviewed scientific journals; and (c) prepare and submit grant applications to NIH and foundations or other scientific organizations.

ARIZONA ALZHEIMER'S CONSORTIUM
2025 – 2026 Scientific Progress Report

Hispanic **E**nrollment in **A**lzheimer's **R**esearch **T**rials (The **H.E.A.R.T.** Program at BNI). Marwan Sabbagh, MD, Anna D. Burke, MD. Barrow Neurological Institute, St. Joseph's Hospital and Medical Center; St. Joseph's Westgate Medical Center; Chandler Regional Medical Center; Mercy Gilbert Medical Center; Arizona Alzheimer's Consortium.

Specific Aims:

1. Implementation of the HEART Program includes a formal development plan outlining internal and external outreach strategies to increase recruitment and the establishment of organizational infrastructure, resources, and written translational materials to promote trial retention while recognizing unmet needs of a large Spanish-speaking community seeking care within Maricopa County.

2. To forge a close working relationship with members of our Hispanic community to formalize the HEART outreach program to increase Alzheimer's disease awareness while addressing clinical research opportunities and family/caregiver support needs to increase trial retention through novel service-related solutions.

3. To create and refine BNI's offerings related to Spanish-language memory screening events and outreach activities.

Background and Significance:

Hispanic persons facing the problem of Alzheimer's disease (AD) constitute an underserved and understudied population in the United States. BNI has partnered with various organizations in the community to help address the educational and clinical needs of patients and families and to demonstrate to this underserved community our strong interest in understanding the unique factors affecting their cognitive health.

Preliminary Data, Experimental Design and Methods:

The HEART Program's outreach objective is designed around an internal (within BNI and Dignity Health opportunities) and an external outreach plan (community) for recruitment, with an established recruiter training program, metrics, and goals to maximize engagement among the Hispanic community. Our retention plan includes focused translational tools (such as Spanish translated rating scales and educational materials) and expanded training among research team personnel offered by Promotores and Hispanic Community Stakeholders to address unique cultural needs. The HEART Program plans to recruit participants from the community through education, outreach, and various events such as memory screenings.

To support the core in recruiting, enrolling, and retaining 50 participants in the Arizona Alzheimer's Disease Research Center (ADRC) study, we will attend community events celebrating Hispanic culture, develop written culturally sensitive educational materials, in both English and Spanish to expand our reach, and partner with various agencies serving both English and Spanish-speaking Latino seniors.

Proposed One-Year and Long-Term Outcomes:

The HEART Program plans to recruit participants from the community through education, outreach, and various events such as memory screenings. To support the core in recruiting, enrolling, and retaining Hispanic participants, we will attend community events celebrating Hispanic culture, develop written materials, including a caregiver dementia handbook, in both

English and Spanish to expand our reach, and partner with various agencies serving both English and Spanish speaking Latino seniors.

An outline of BNI's specific aims to achieve the above-stated enrollment and retention goals includes:

1. Enrollment of 10-15 additional Hispanic study participants over the next year
2. Eventual retention of 50 enrollees in the consortium's clinical core (including current and future Hispanic participants).
3. Development of culturally sensitive dementia related educational materials including tip sheets for various dementia related symptoms
4. Quarterly memory screens targeted for Spanish and English speaking Hispanic populations
5. Outreach events dedicated to the Hispanic population, such as Spanish speaking memory cafes
6. Continued focus on building a diverse study team including retention of multiple coordinators who are bilingual in English/Spanish as well as a full time psychometrist who is also bilingual and has significant experience with performing the cognitive testing in Spanish.

Year End Progress Summary:
The HEART Program within the Alzheimer's Disease and Memory Disorders Division of Barrow Neurological Institute, under the direction of Marwan Sabbagh, MD and Anna Burke, MD, was originally designed to increase recruitment and retention of Hispanic subjects in the Arizona Alzheimer's Disease Research Center (ADRC). The goal was to remove unique cultural barriers and increasing awareness and access to meet the defined program goals.
Early in the FY26 funding period, but after the HEART proposal had already been accepted & funds were awarded, a joint decision was made between BNI & ADRC leadership to discontinue BNI's participation in the ADRC study following the FY26 funding period. In order to effectively transition participants to other ADRC sites, BNI halted enrollment of new participants and pivoted focus to completing any follow up visits due before April 1, 2026 and transferring study participants to other sites. Due to this change in the expected interaction of HEART and the ADRC study, BNI focused its engagement & outreach efforts with the Hispanic community toward other research-related endeavors. As such, the ADRC enrollment and retention related "Specific Aims" from the initial proposal were not able to be pursued this year.
1. Similar to the prior funding period, over the course of the 2025-2026 fiscal year, BNI successfully retained all of the existing bilingual team members, including the full-time bilingual research psychometrist. The retention of our considerable pool of Spanish speaking staff members continues to significantly enhance our ability to reach community members, retain existing participants and gather more accurate data.
2. The addition of funding to support outreach personnel has been a significant advantage to this project in FY26. On September 23, 2025 BNI held a Spanish-language memory screening event where we were joined by 22 community members. This event was wholly supported by the funds provided by the HEART Project & testing was performed by the bilingual members of our staff – all of whom had previously received training on administration on the Montreal Cognitive Assessment in Spanish.
3. The outreach support provided by the HEART grant has also allowed us to attend many other events that were aimed at engaging the Hispanic/Latine' community including:
- The AZ Hispanic Chamber of Commerce's Annual Community Health Fair on July 26, 2025 (800+ attendees)

- National Tribal Health Conference Resource Fair on September 9-11, 2025 (1000+ attendees, 10% of whom identified as Hispanic/Latino)
- The “Movimiento” Family Fun Run + Resource Fair on October 18, 2025 (300+ attendees)
- Fall Health Resource Fair – Unlimited Potential on October 25, 2025 (432 attendees)
- MLK Day Celebration Festival + Resource Fair on January 19, 2026 (1000+ attendees)
- Spring Health Resource Fair – Unlimited Potential on March 28, 2026 (200+ attendees)
- “Ventanilla de Salud” resource table at the Mexican Consulate on April 14, 2026 (53 attendees)

4. The funds also allowed BNI to continue internal Spanish-language programming events including:
- Spanish Language “Mitos de la Demencia” (“Dementia Myths”) presentation on August 21, 2025 (23 attendees)
- Spanish Language Forum & Resource Fair: “Junto Planificando El Futuro” Care Planning Forum on February 28, 2026 (31 attendees)
- Spanish Language “Cafecito y Comunidad” community presentation & resources on April 21, 2026 (86 attendees)

5. BNI has continued our practice of ensuring that all ADRD trials being conducted at Barrow have Spanish language consents available when allowable per study protocol. We continue to request Spanish-language study materials during the study startup phase of all new trials. This initiative to obtain Spanish language materials from as many new study sponsors as possible is intended to enhance our portfolio of study options for those whose primary or preferred language is Spanish. This will also ensure that potential participants who may benefit from participating in clinical research are not being lost simply due to a lack of information available for them to read.

6. As part of our goal to ensure Spanish language educational materials are available to our patients & study participants, we paid for professional translation of several informational flyers for Project Pegasus. Project Pegasus is a research project that partners with Primary Care Providers to identify patients at earlier stages of cognitive impairment for referral to a cognitive specialist. This included several NIH-provided documents that had not previously been available in Spanish (done with NIH approval to modify, of course).

As Barrow Neurological Institute looks ahead to what lies in store for next year there is no doubt that the diligent and consistent efforts put forth by the staff, who strive to improve the lives of our Hispanic patients and community members, will remain invaluable. Barrow’s dedication to enhancing not only the number of Hispanic patients interacted with but, perhaps more importantly, the quality of those interactions will prove crucial in reaching its goal of establishing and maintaining deep community ties.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

The role of an aberrant synaptome in microglia-associated synaptic pruning in C9orf72-FTD. Rita Sattler, PhD. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Specific Aims:

Aim 1: Establish the cellular and molecular synaptic changes in *C9orf72*-FTD using *ex vivo* and *in vitro* human model systems. Human postmortem frontal and occipital cortex tissue from 10 C9-FTD cases and 10 matched controls will be used to generate synaptosome preparations for RNA sequencing and proteomics analyses. In parallel, hiPSC-derived cortical neurons (hiPSC-CNs) will be generated from 4 C9-FTD lines, 4 controls, and one isogenic pair. Synaptosomes will be collected at three differentiation stages (DIV60, 80, 100) for temporal multi-omics profiling. Findings will be validated by western blot and qRT-PCR analyses of synaptosomal proteins and RNAs.

Aim 2: Determine whether an aberrant synaptome regulates microglia activity and synaptic pruning. To distinguish whether synaptic alterations or intrinsic microglial changes drive synapse elimination, we will perform iPSC co-culture experiments combining diseased and control neurons and microglia in all conditions. Microglial engulfment of synaptic proteins will be assessed by immunostaining, and neuronal activity measured using MEA. In parallel, pHrodo-labelled synaptosomes from diseased and control neurons will be applied to microglia to quantify phagocytosis rates.

Background and Significance:

Synaptopathy in C9orf72-FTD. Synaptic dysfunction (synaptopathy) is a key early feature of neurodegenerative diseases, including AD, FTD, and ALS. Evidence from mouse models and human tissue indicates synaptic alterations in ALS/FTD, including C9orf72 mutation carriers. C9orf72 localizes to synaptic compartments and is implicated in vesicle trafficking. Haploinsufficiency reduces expression of synaptic proteins such as synapsin, synaptotagmin, and Rab39b, leading to altered glutamate receptor regulation. While limited studies suggest synaptome alterations in C9-FTD, a comprehensive characterization of RNA and protein changes at human cortical synapses is lacking.

Microglia and synaptic dysfunction. Microglia are essential for synaptic refinement during development, removing inactive synapses to maintain network function. Similar mechanisms are implicated in neurodegeneration, including AD and FTD, but remain poorly understood at the molecular level. Few studies have examined disease-associated synaptome changes in humans. A more comprehensive analysis is needed to determine how altered synapses signal to microglia and whether aberrant pruning contributes to pathology in C9orf72-FTD, potentially identifying new therapeutic targets.

Experimental Design and Methods:

Specific Aim 1

Detailed Methods

Synaptosome preparation from human postmortem brain tissue samples. Synaptosomes will be prepared as described, wherein the tissue is homogenized in a lysis buffer and centrifuged to separate the cell debris and cytosol. Further centrifugation will separate this cytosol into a crude synaptosomal pellet containing pre- and post-synaptic compartments, which we refer to as synaptosomes.

Multi-omics analyses of synaptosome preparations: Synaptosomes will be submitted for proteomics and bulk RNAseq transcriptomics profiling at the TGen core facilities.

Differentiation of iPSC-CN: Following a previously published protocol, iPSC will be differentiated into CNs To quality control the desired cortical cell-type, the cells will be labeled with SATB2 or TBR1, markers of neurons in upper and deep cortical layers, respectively.
Synaptosome generation from iPSC-CNs: At DIV 60, 80, 100, we will isolate synaptosome fractions from iPSC-CN cultures as described above for the human tissue analyses.

Specific Aim 2
Detailed Methods
Differentiation of iPSC-MG: iPSCs will be differentiated into microglia, co-cultured with DIV90 iPSC-CNs and maintained for 2 weeks. These cocultures will be established following the protocol from a recent publication on iPSC-MN and iPSC-MG. The initial plating ratio will be 1:1=MG:CN. Cultures will be plated on coverslips for immunohistochemistry and 48-well MEA plates to measure neuronal firing.
Measurements of neuronal excitability. iPSC-CN-MG cocultures will be grown in special 48-well plates to follow neuronal activity using a micro-electrode array MEA platform (Maestro Axion Biosystems). Recordings of network firing, spikes and bursting patterns will be measured daily during the time of co-culturing, up to 6 weeks, as shown in our previous publication. Electrical activity will be analyzed using Axis 2.0 software.
Microglia engulfment of neuronal synapses. To examine the engulfment of synapses by microglia in the iPSC-cocultures, we will perform co-labeling of synaptic and microglia markers, such as synaptophysin and PSD-95 and TREM2 or Iba1, respectively, as shown in our recent publication. We will also label microglia for co-localization of complement marker, C1q, and synaptic marker proteins, based on the role of complement in synapse loss in AD mouse models. Immunostaining will be analyzed using confocal microscopy with Zeiss Airyscan high resolution settings.
Measurements of synaptosome phagocytosis: We will pH-rodo label C9 and control iPSC-CN synaptosomes as described in our previous studies and elsewhere and expose iPSC-MG mono-cultures (disease and control, DIV 38) to these labeled synaptosomes. We will perform live fluorescent imaging and quantify uptake kinetics and fluorescence intensity of the engulfed cargo.

Proposed One-Year and Long-Term Outcomes: These exploratory studies will enable us to thoroughly assess the protein and RNA changes observed at the synaptic compartment in the context of C9-FTD in both, patient brain tissue and a human iPSC-based neuronal model system. Furthermore, the in vitro system will provide us with the opportunity to assess whether microglia contribute to these synaptic aberrations by co-culturing neurons with diseased or healthy iPSC microglia. The results of these studies will serve as preliminary data for a larger federal grant application to either the NIH or the DOD in which we will propose to assess the functional consequences of synaptic changes in C9-FTD and the role of microglia in this pathological process.

Year End Progress Summary:
Completed aspects of our studies:
Specific Aim 1
Mutli-omics analysis of C9-FTD patient postmortem brain tissue and iPSC-cortical neuron synaptosome preparations. We successfully isolated synaptosomes from frontal cortex postmortem tissue of C9-FTD (n=10) and age-matched controls (n=10), in addition to patient-derived iPSC-cortical neurons from C9-FTD (N=3) and non-neurological disease controls (N=3). Transmission Electron Micrography of isolated synaptosomes confirmed intact synaptosome preparations showing pre- and postsynaptic organelle and structures, including synaptic vesicle and postsynaptic densities. After RNA sequencing and proteomics analyses of the homogenate (H0) and synaptosome (P2) fractions across control and C9-FTD cases (brain and iPSC neurons), Principal Component Analysis (PCA) confirmed sample separation by biochemical fraction

identity both on the protein and RNA level. In addition, we generated a Z-score-normalized heatmap of synaptic protein abundance across H0 and P2 fractions in control and C9-FTD cases, highlighting enrichment of synaptic gene sets in the P2 fraction and nuclear gene set enrichment in the H0 fraction.

Proteomic analyses. Quantiative differential protein expresssions analysis revealed significant protein expressions in both H0 and P2 fractions, with 1,324 differentially expressed proteins (DEPs) in the C9-FTD brain synaptosomes (a total of 555 proteins were significantly upregulated, and 769 proteins were downregulated ($p=<0.05$, *t-test*)). The C9-FTD iPSC-neuron synaptosomes revealed 962 DEPs, 508 proteins being significantly upregulated, and 454 proteins significantly downregulated ($p=<0.05$, *t-test*). SYNGO Biological Process enrichment analysis of significantly upregulated and downregulated proteins in brain tissue synaptosome fractions revealed pathways associated with downregulated proteins, including synaptic vesicle cycle, trans-synaptic signaling and synapse assembly as well as pathways associated with upregulated proteins, including postsynaptic actin cytoskeleton organization. Some, but not all of these pathways were also identified from the iPSC-neuron synaptosome pathway analysis.

Transcriptomic analyses. Similar changes were observed on the RNA level with 2,835 differentially expressed genes (DEG) in C9-FTD brain synaptosomes (a total of 1,763 genes were significantly upregulated, and 1,072 genes were downregulated (DESeq2 Wald test, Benjamini-Hochberg adjusted $p<0.05$)), and 402 DEGs in C9-FTD iPSC cortical neuron synaptosomes (a total of 138 genes were significantly upregulated, and 264 genes were downregulated (DESeq2 Wald test, Benjamini-Hochberg adjusted $p<0.05$)).

An interesting finding from the RNA seq analyses was the presence of TDP-43 associated CE containing RNAs at the synapse. This is the first time that CE-including RNAs were reported to be at the synaptic compartment, in addition to the nuclear compartment, where splicing primarily occurs. These findings opened up a new avenue of investigation in the lab and has already lead to the submission of a R21 application to the NIH.

Integration of brain tissue and iPSC omics data. Integrating RNA and protein level changes within each human model system and between model systems revealed that on the RNA and protein level, significant overlapping DEGs and DEPs were found in pathways associated with synapse organization, regulation of synaptic assembly and transsynaptic signaling, supporting the relevance of the iPSC-cortical neuron culture for disease modeling.

Specific Aim 2

Neuron-microglia co-cultures. We have successfully established a neuron-microglia coculture, with preliminary data supporting effects of MG on neuronal firing. We also optimized the MG phagocytosis assays.

To be completed:

Specific Aim 2.

We are currently culturing iPSC neurons and MG for the proposed co-cultures, and have all of the labeled pHrodo synaptosomes preparations generated to perform MG phagocytosis on Ctrl vs C9-FTD synaptosome preparations.

Challenges

Co-culture conditions were difficult to replicate from published papers hence had to do a lot more optimization steps.

CRITICAL PATH INSTITUTE
PROJECT PROGRESS REPORT

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Longitudinal NULISAseq profiling of CSF and plasma biomarkers in PSEN1 E280A mutation carriers. Yashmin Karten, PhD, Diane Stephenson PhD, Nicholas Ashton, PhD, Nicholas Henscheid, PhD, Marissa Denkinger PhD. Critical Path Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Specific Aims:

Aim 1: To determine whether longitudinal biomarker signatures measured by NULISAseq predict amyloid accumulation and how these predictors are different between trial arms.

Aim 2: To examine which cumulative proteomic patterns best predict downstream tau deposition and regional brain atrophy over time, and to assess how these fluid–imaging relationships are different between arms.

Background and Significance:

Sensitive, minimally invasive biofluid biomarkers are critical for Alzheimer's disease (AD) research, enabling detection of pathology before clinical symptoms emerge and monitoring response to therapies. While biomarkers such as pTau217 demonstrate strong diagnostic accuracy for amyloid positivity and AD and correlate with amyloid and tau PET imaging, they do not capture other disease processes including inflammation, vascular pathology, and synucleinopathy. Traditional immunoassays are limited in scope, measuring only a small number of analytes per run.

NULISAseq addresses this limitation by enabling high-throughput, ultra-sensitive measurement of approximately 130 CNS-relevant proteins from small CSF or plasma volumes. This allows simultaneous detection of low-abundance biomarkers, including phosphorylated tau isoforms, neurofilament light chain, synaptic proteins, and cytokines, facilitating characterization of complex, multipathway biomarker signatures.

The Colombia API ADAD Trial generated a unique longitudinal biobank of CSF, plasma, imaging, and clinical data. Applying NULISAseq to these samples will support identification of fluid biomarkers associated with amyloid accumulation, conversion to mild cognitive impairment, and downstream tau and atrophy changes. Building on prior CPAD work modeling tau PET progression across brain regions using linear mixed-effects models, this project proposes incorporating fluid biomarkers to enhance disease progression models and improve understanding of AD mechanisms, while informing the design of future prevention and treatment trials.

Preliminary Data, Experimental Design and Methods:

Previous analyses of plasma samples from the API ADAD cohort using Roche Elecsys© and NeuroToolKit assays showed that untreated mutation carriers had elevated baseline plasma Aβ42/40 levels independent of age or amyloid plaque burden and exhibited stronger age-related increases in pTau181, pTau217, NfL, and GFAP. Longitudinal increases in these biomarkers were also observed. Crenezumab-treated carriers showed increases in plasma Aβ42 and Aβ40, but no significant treatment effects on other plasma biomarkers, including pTau, NfL, GFAP, YKL-40, or sTREM2.

The proposed study includes 36 non-carriers receiving placebo, 41 carriers receiving placebo, and 47 carriers receiving crenezumab from the API ADAD trial. Participants contributed longitudinal CSF and plasma samples collected at baseline and follow-up visits over 4–5 years, along with PET and MRI imaging and cognitive assessments.

Stored CSF samples at Banner Sun Health Research Institute were analyzed using the Alamar NULISAseq CNS Disease Panel to measure approximately 130 neurodegeneration-related biomarkers.

Proposed One-Year and Long-Term Outcomes:

Integrating biomarkers into existing mixed effects models will help elucidate the biological role of ADAD and identify strong predictors of subsequent amyloid PET SUVR increases across trial arms. LASSO regression is expected to identify a specific subset of inflammatory markers whose early changes correlate robustly with later regional tau accumulation patterns. We anticipate that principal component analysis will reveal distinct protein clusters reflecting separate biological processes (synaptic integrity, inflammation, and amyloid processing) that demonstrate differential responses based on trial arm. Hierarchical clustering of longitudinal biomarker trajectories should identify patient subgroups with similar progression patterns, potentially revealing different disease progression based on molecular signatures. Time-lagged correlation analyses between fluid biomarkers and imaging metrics will likely establish the temporal sequence of pathological changes, with specific NULISAseq protein alterations preceding detectable PET and MRI changes.

A future aim is to examine whether changes in NULISAseq measured proteins between baseline and future timepoints predict participants who convert to MCI over the course of the study from those who remain cognitively stable. We will compute individual change scores for each of the ~130 proteins in CSF and plasma, then apply dimensionality reduction techniques such as principal component analysis (PCA) or regularized regression methods (LASSO) to select a panel of biomarker predictors and estimate their associations with cognitive outcomes. By comparing the selected biomarkers and model performance across different participant groups, we will assess how these fluid markers relate to disease progression.

Year End Progress Summary:

The Colombia Alzheimer's Prevention Initiative (Colombia API) ADAD Trial represents a flagship learning study that has generated invaluable insights into predictive biomarkers for Alzheimer's disease prevention through the longitudinal evaluation of a unique, well-characterized cohort with genetically defined Alzheimer's disease. C-Path's AD consortium CPAD has keen interest to learn from this st and other genetically defined populations to allow data driven and innovative regulatory strategies that focus on early intervention. Over the past 2 years, CPAD has focused on developing harmonized methodologies for tauPET neuroimaging and methodologies with growing interest in multimodal biomarker and modeling strategies. The NULISA Alamar platform has emerged as a leading proteomic panel being applied across neurodegenerative disorders including dementias. The API study and unique leading expertise of Banner core biomarker center of excellence provides a unique opportunity to focus this year on generating rich data to inform biomarker modeling strategies for the future.

The Columbia API study enrolled 252 cognitively unimpaired carriers alongside non-carrier relatives, and randomized carriers to crenezumab treatment or placebo over the course of five years[1]. Although crenezumab did not significantly slow cognitive decline, numerical trends across several endpoints suggest potential biological effects that remain incompletely understood. In this proposed study, we will leverage the longitudinal CSF NULISAseq data already generated from baseline and follow-up visits across the three Colombia API trial arms

Stored cerebrospinal fluid (CSF) samples from the Colombia API Trial were successfully prepared and analyzed using the Alamar NULISAseq CNS 120 Disease Panel. The assay was applied to longitudinal CSF samples from PSEN1 E280A mutation carriers and non-carriers, including

participants randomized to placebo or crenezumab, to generate high-dimensional proteomic profiles across approximately 130 CNS-relevant biomarkers. These measurements include phosphorylated tau species, neurodegeneration markers, synaptic proteins, inflammatory markers, and other proteins relevant to Alzheimer's disease biology. Completion of the CSF NULISAseq assay represents an important milestone toward the proposed goal of integrating fluid biomarker signatures with longitudinal amyloid PET, tau PET, MRI, and clinical outcomes from the API ADAD cohort.

The resulting NULISAseq dataset provides a unique opportunity to evaluate whether baseline levels and longitudinal changes in CSF proteins are associated with amyloid accumulation, downstream tau deposition, regional brain atrophy, and clinical progression. Ongoing work is focused on quality control, harmonization of the NULISAseq data with existing imaging, clinical, and treatment-arm datasets, and development of analytic models to identify proteomic signatures associated with disease progression and potential treatment-related differences.

The analytic modeling strategy will combine longitudinal statistical modeling with high-dimensional feature-selection approaches. Initial analyses will characterize individual protein trajectories and associations with clinical, imaging, and fluid-biomarker outcomes using regression and mixed-effects modeling frameworks that account for repeated measures, time, carrier status, treatment assignment, and other relevant covariates. To address the high dimensionality and correlation structure of the NULISAseq panel, penalized regression methods, including LASSO-type models, will be used to identify sparse multivariable protein signatures associated with future cognitive decline, tau PET progression, amyloid burden, regional atrophy, or other disease-relevant outcomes. This approach is intended to move beyond single-marker analyses by selecting combinations of proteins that jointly improve prediction or explain variation in downstream disease measures.

Candidate modeling workflows will include baseline-protein models for predicting subsequent change in cognition or imaging biomarkers, longitudinal models incorporating protein change over time, and sensitivity analyses comparing protein-only models with models that include established covariates and conventional Alzheimer's disease biomarkers. Cross-validation or related internal validation procedures will be used to evaluate model stability, predictive performance, and robustness of selected protein signatures. The planned approach is conceptually aligned with recent ADAD CSF proteomics work showing that LASSO-based feature selection can identify compact proteomic signatures with predictive value for mutation status and clinical stage, while recognizing that the present API analyses will focus specifically on the Colombia trial cohort, NULISAseq CNS 120 analytes, longitudinal outcomes, and potential treatment-related effects.

These analyses will support the proposed one-year and long-term objectives, including the identification of proteomic patterns that may precede, predict, or track imaging and cognitive changes in autosomal dominant Alzheimer's disease. More broadly, the work will help determine whether targeted CSF proteomic profiles can provide interpretable biomarker signatures for disease staging, progression modeling, and future therapeutic-response analyses in ADAD. The collaboration between C-Path, Banner Alzheimer's Institute, the Arizona Alzheimer's Consortium, and the NULISA assay team has established the foundation for future analyses, manuscripts, and potential grant applications leveraging this longitudinal fluid biomarker and imaging resource.

MAYO CLINIC ARIZONA
PROJECT PROGRESS REPORT

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Project Progress Report

Normal and Pathological Aging (Preclinical Alzheimer's Disease). Bryan K. Woodruff, MD, Richard J. Caselli, MD, Dona E.C. Locke, PhD. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Project Description:
Cognitively normal individuals age 21-99 (most age 45-70) undergo 1) APOE genotyping to categorize their relative risk for developing Alzheimer's disease; 2) longitudinal neuropsychological and behavioral assessments; and 3) serve to create a biorepository for DNA, serum, plasma, viable frozen lymphocytes, and immortalized cell lines to determine what factors divert individuals from normal to pathological aging/Alzheimer's disease with the intent of identifying optimal timing of treatment and new potential therapeutic targets for preventing this divergence (prevention of Alzheimer's disease). This "APOE Cohort" also serves as a core resource for multiple collaborative projects within our site and for the consortium.

Specific Aims:
A. To maintain and grow a unique cohort of human aging in which we characterize the effect of APOE gene dose (a risk factor for Alzheimer's disease) on age-related changes in:

1. Mentation (neuropsychological measures of cognition and behavior; subjective assessments by observers and self; sleep parameters)
2. Brain Imaging (structural brain changes [MRI], functional [FDG-PET], amyloid-PET, tau-PET)

B. To correlate longitudinal changes on each of these measures with clinical outcomes (mild cognitive impairment, Alzheimer's dementia, non-Alzheimer's dementia)
C. To characterize the influence of other demographic, genetic, epigenetic, and health factors on cognitive aging trajectories
D. To create a biobank of serum, plasma, DNA, frozen viable lymphocytes, and immortalized cell lines of this cohort.
E. To function as a core resource collaboratively supporting other investigators
F. To support, where appropriate, activities of the NIA funded Arizona Alzheimer's Disease Center

Background and Significance:
Even at the earliest clinical stages of Alzheimer's disease (AD), amyloid pathology has nearly peaked yet neither symptoms nor brain atrophy correlate well with amyloid burden. The modest benefits of current anti-amyloid therapies may be related to delay in initiation, prompting study of an array of treatment strategies that begin during the preclinical, asymptomatic stage. Our work to date has helped to define and characterize the preclinical stage of AD, differentiating normal from pathological aging. Themes of our current research include 1) identification of preclinical disease modifying attributes (genetic, medical, demographic, and others), 2) extension of preclinical testing and precision medicine into the clinical practice domain, and 3) integration of multiple data sources into predictive algorithms.

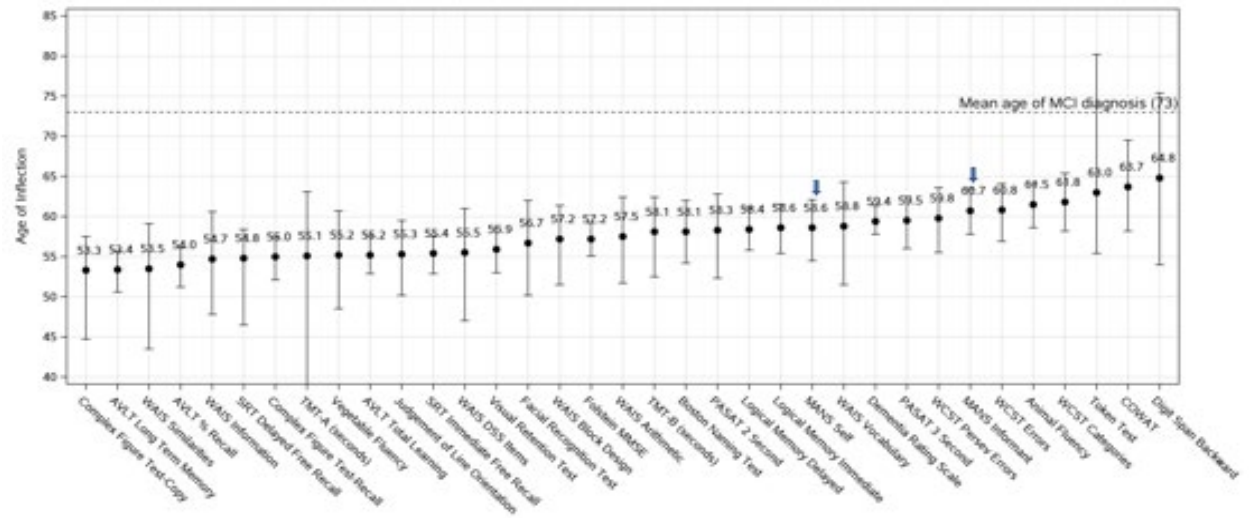
Preliminary Data:
To date we have completed APOE genetic testing on roughly 3400 participants from which were selected our study population for further testing. We have completed one or more epochs of neuropsychological testing on 1176 individuals including 648 APOE e4 noncarriers, 371 e4 heterozygotes, and 139 e4 homozygotes with followup durations of up to 30 years (average just over 10 years) providing data for longitudinal studies. We have over 3500 (combined) plasma

and serum samples on roughly 725 individuals, and DNA on all. 497 have immortalized cell lines established including all with brain imaging. We have completed whole genome sequencing in 956 subjects. MRI enrollment continues, with 198 completed to date. Additional 7T MRI is planned in a carefully selected segment of our cohort. Among our many accomplishments, we established cognitive aging trajectories for each of 3 APOE genotypes (1-3), the differential impact of modifying factors such as cardiovascular risk factors (4) as well as personality factors (such as proneness to stress) (5,6) and subsequently have shown that pre-MCI deviates from normal aging roughly 20 years before incident MCI diagnosis (7).

Proposed One-Year and Long-Term Outcomes:
Specific goals for this next fiscal year include:

1. Maintain continuity of follow-up testing of our established cohort.
2. Expand enrollment as our more limited budget will permit with an emphasis on increasing diversity
3. Expand our biobanking efforts to include all those with young onset Alzheimer's disease
4. Use supporting funds to expand the scope of our work to include whole genome sequencing that will:
    a. Establish an ongoing resource for future research efforts
    b. Allow analysis of polygenic risk scores within this and other longitudinal cohorts
5. Use supporting funds to include MRI studies of cohort members that will:
    a. Establish an ongoing resource for future research efforts
    b. Expand enrollment our initial study examining the correlation of APOE genotype with inter-hemispheric patterns of symmetry of functional MRI resting state in memory and Alzheimer's disease-sensitive regions of interest that reflect areas of early tau and amyloid deposition respectively
    c. Provide a training and educational opportunity for young investigators
6. Provide collaborative support for other scientists
7. Continued evaluation of the utility of a novel eye tracking and mental arithmetic task (OCAT) to predict which cognitively normal individuals are at higher risk for developing cognitive decline.

Year End Progress Summary:
1. The results of our cognitive and behavioral aging trajectories contrasting individuals who developed incident MCI with those remaining clinically normal showed that the earliest cognitive changes predate incident MCI diagnosis by 20 years (figure), rivalling the earliest biomarker changes and implying that current pathophysiological models which posit a linear sequence of change with cognition lagging are in need of revision (7).



2. Based on our work to date and related studies from the scientific literature we published the amyloid homeostasis hypothesis, an alternate interpretation of the role of amyloid in the pathogenesis of Alzheimer's disease, one that better accounts for the critical physiological roles played by amyloid precursor protein and its various fragments, including abeta peptide and the modest benefit of current amyloid targeted therapies (8).
3. We provide collaborative support to multiple investigators at Arizona State University (Yalin Wang, Blair Braden, David Brafman, Michael Sierks, Molly Maxfield, Li Liu), USC (Berislav Zlokovic), Mayo Clinic (Oana Dumitrascu, Dona Locke, Guarav Pradhan, Otto Pedraza, Leslie Baxter, Cynthia Stonnington), and Banner Alzheimer Institute (Eric Reiman and his team).
4. Utilizing diffusion-weighted magnetic resonance imaging and volumetric assessments, we identified that hippocampal microstructural measures positively correlated with verbal recall in APOE epsilon4 carriers, not evident on volumetric assessments (9).
5. The Oculo-Cognitive Addition Test (OCAT) measures oculometric features during mental addition tasks in under one minute. Utilizing machine learning models, it accurately predicts DRS outcomes in our cohort and has the potential to serve as a practical and scalable cognitive screening tool to identify individuals experiencing subtle cognitive decline (10).

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MIDWESTERN UNIVERSITY
PROJECT PROGRESS REPORTS

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Assessment of inflammatory pathways involved in the brain-intestinal axis in western diet induced Alzheimer's pathology. Layla Al-Nakkash, PhD and Tom Broderick, PhD. Department of Physiology, Midwestern University; Arizona Alzheimer's Consortium.

Specific Aims:

1. Determine ability of exercise to modify the brain inflammation of HFHS fed male mice.
2. Determine ability of exercise to modify the intestinal inflammation of HFHS fed male mice.

Background and Significance:

Obesity resulting from ingestion of high energy foods such as high-fat diet, results in loss of learning and memory function. In male C57BL/6J mice, HFD induced cognitive deteriorations mediated via neuronal insulin resistance and brain mitochondrial dysfunction. Metabolic syndrome is a major contributor towards cardiovascular disease, type II diabetes, insulin resistance and inflammation, which are all risk factors for Alzheimer's Disease (AD) and dementia. Such dietary habits are correlated with increased deposition of amyloid beta, increased formation of neurofibrillary tangles and reductions in synaptic plasticity. Clinically, given the epidemic of obesity in the US, this proposed study is merited. Although the adverse effects of obesity are well-known, its underlying mechanisms remain to be determined. Feeding mice a high fat high sugar diet (HFHS) has been shown to negatively influence, i.e. increase prevalence of brain markers of AD. For example, a recent study demonstrated that male mice fed HFHS showed increased microgliosis as measured by IBA-1 fluorescence, indicative of an amplified neuroinflammatory environment.

Exercise is commonly recommended by physicians to assist in reversing obesity. Of relevance to this proposal, exercise has been shown to improve hippocampal-dependent learning and memory in older individuals. Indeed, voluntary wheel running has been shown to ameliorate some of the memory dysfunction in HFD female C37BL/6J mice. Skeletal muscle is a key secretory organ, releasing bioactive molecules known as myokines that communicate metabolic and proteotoxic changes to the CNS. In usual healthy circumstances exercise can play a major role in maintenance of neurocognitive function which results in benefits for cognition and memory. Exercise has also been shown to stimulate hippocampal neurogenesis and increase brain derived neurotrophic factor levels.

Preliminary Data, Experimental Design and Methods:

We used brain, and small intestines (jejunum) already collected and maintained at -80°C, from the murine groups shown below. Forty male *C57BL/6J* mice were purchased from Charles River Labs (aged 4-weeks), acclimated for 1-week, and then separated into one of four groups for the 12 week study duration: (1) lean-sedentary controls (fed normal chow and water), (2) lean-exercised, (3) HFHS-sedentary (fed high fat diet containing: 60% fat, 20% protein and 20% carbohydrate from Dyets Inc) along with 42 g/L liquid sugar (sucrose and fructose combined, HFHS diet induced diabetic obesity is induced at ~9-10 weeks). & (4) HFHS-exercised. Exercise duration was set at 30 min/day for 5 days/week, for the 12-week study. Exercise intensity was 12 meters/min (i.e., the American Heart Association guidelines for 30 minutes of moderate activity, for a total of 150 minutes/week). This study was approved by the MWU IACUC (#4205).

Proposed One-Year and Long-Term Outcomes:

Proposed expected outcomes:

1. We predict that brain inflammatory state will primarily be modified with HFHS diet (upregulated) and downregulated with exercise.
2. We predict that intestinal inflammatory state will primarily be modified with HFHS diet (upregulated) and downregulated with exercise.

The results obtained from this proposal will provide focused pathway-driven mechanistic directions with the inclusion of inflammatory data for a future extramural grant submission that is more pathway focused, versus a fishing expedition. It is key to note that the data generated from the proposed study, could be a stand-alone manuscript correlating the gut-brain inflammatory state, or dependent on reviewer suggestions, could be included with the data generated from the last years MAAC study to develop more mechanistic papers.

Year End Progress Summary:

Aim 1. Determine ability of exercise to modify brain inflammation of HFHS fed male mice. At euthanasia, each murine brain was extracted and the hippocampus removed and immediately frozen in liquid nitrogen and maintained at -80°C for the following studies. We evaluated a series of cytokines in hippocampus homogenate. We found no differences between the four groups in the following cytokines: GM-CSF, IFN-Gamma, Il-2 and MCP1. Interestingly, we found that HFHS significantly decreased Hippocampus Il-12p70 levels compared to Lean sedentary controls (no exercise effects) and exercise significantly decreased Il-10 levels in HFHS fed mice, but had no effect in leans.

Aim 2. Determine ability of exercise to modify intestinal inflammation of HFHS fed male mice. Sections of small intestine (jejunum) were extracted at euthanasia, frozen for inflammation analyses. We evaluated a series of cytokines in jejunum homogenate. We found that HFHS diet induced the following changes: significantly increased levels of Il-1B, Il-6, KC, and significantly decreased levels of jejunum Il-10. In lean mice, exercise significantly increased levels of IFN-Gamma, Il-6 and MIP-2, and in HFHS fed mice exercise significantly decreased levels of Il-1B.

Thus, cytokine changes were not comparable in brain tissue and intestinal tissue either between lean sedentary and HFHS sedentary and moreover exercise-induced changes were not correlated between the two tissues.

Future grant applications: We anticipate a possible extramural grant application during this next AY: perhaps to the AAC or Diabetes Action and research Education Foundation.

Future publications: We anticipate submission of one manuscript by the end of summer using data from this MAAC funded proposal.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Oxidative stress causes increased amyloid peptide levels through telomeric protein, RAP1.

Nancy Bae, PhD and Mark J. Swanson, PhD. Department of Biochemistry and Molecular Genetics, Midwestern University; Arizona Alzheimer's Consortium.

Specific Aims:

Aim 1: Investigate the relationship between oxidative condition and amyloid peptide production.
Aim 2: Identify the target genes of RAP1 and TET3 that might influence Aβ peptide production

Background and Significance:

Although Aβ deposition is a hallmark of the disease, the molecular mechanisms driving plaque formation is not fully understood. One possible contributor to Aβ deposition, a hallmark of Alzheimer's disease (AD), is dysregulation of gene expression that increases Aβ production. Amyloid precursor protein (APP) is a transmembrane protein that is sequentially cleaved by β-secretase and γ-secretase, whose catalytic core contains presenilins 1 and 2 (PS1 and PS2). Mutations in APP, PSEN1, or PSEN2 cause early-onset familial AD by increasing production of the neurotoxic Aβ42 peptide relative to the more soluble Aβ40 form. Nielsen et al. (2002) demonstrated that PS1 specifically interacts with the epsilon isoform of glial fibrillary acidic protein (GFAPε), suggesting that it is a potential regulator of γ-secretase activity. Aβ42 has been shown to induce ROS production, linking amyloid pathology with oxidative stress.

Telomeres are maintained by the shelterin complex that includes RAP1 (TERF2IP). While RAP1 is recruited to telomeres by TRF2, studies indicate that RAP1 also performs non-telomeric functions. Using a yeast two-hybrid screen, we identified RAP1 as a binding partner of GFAPε, suggesting a connection between telomere biology and AD-associated pathways.

Oxidative stress (OS) and Aβ accumulation appear to reinforce one another in AD pathology. OS has been implicated in age-related telomere shortening; thus, age-related loss of telomere protection may influence disease progression. Our previous work demonstrated that OS induces RAP1 translocation from the nucleus to the cytoplasm (Swanson et al., 2016). We further showed that RAP1 interacts with GFAPε and PS1 to form a trimeric complex and that RAP1 enhances γ-secretase activity, an effect that is strengthened by GFAPε (Swanson et al., 2023). These findings suggest a mechanism by which oxidative stress could increase Aβ production.

We also identified TET3 as a RAP1-interacting protein. TET3 catalyzes the conversion of 5-methylcytosine to 5-hydroxymethylcytosine, initiating DNA demethylation and promoting gene activation. TET3 is recruited to chromatin by REST, a transcriptional regulator whose loss is associated with cognitive impairment. Importantly, TET proteins also contribute to telomere maintenance, as their deletion results in telomere dysfunction and chromosome instability. Because neuronal TET3 does not directly bind DNA, and our data indicate that RAP1 can bind DNA outside telomeres, we hypothesize that RAP1 recruits TET3 to non-telomeric genomic sites to regulate gene expression that influences Aβ peptide production.

Preliminary Data:

Human U251 glioblastoma cells were grown and serum-starved for 48 hours to introduce OS. RAP1 levels were measured via immunoblotting, and we observed a 2-fold increase in RAP1. The media were analyzed for secreted Aβ40 and Aβ42 levels by ELISA. There was a ~6-fold increase in Aβ40 and a ~1.1-fold increase in Aβ42 levels in cells grown in no-serum conditions. A total of 18 independent samples per condition were tested, and the results were consistent: RAP1 expression was elevated in no-serum conditions, and the Aβ levels were elevated as well.

Recombinant RAP1 and TET3 were expressed in bacteria, with interaction confirmed by affinity chromatography. Since TET3 deficiency has been associated with neurodevelopmental

disorders, we hypothesize that nuclear RAP1 interacts with TET3 to induce Aβ peptide production, especially under cellular stress. Through a literature search, we identified 13 RAP1 targets, 14 TET3 targets, and 6 REST target genes. Primers for RT-qPCR were designed and validated using RNA from SH-SY5Y and U251 cells. The 18S and GAPDH primers were used as controls.

Experimental Design and Methods:

Aim 1: Investigate the relationship between oxidative stress and amyloid peptide production

1a. Measure γ-secretase activity: Serum deprivation increases RAP1 and Aβ levels. We hypothesize that elevated RAP1 promotes Aβ production by enhancing γ-secretase activity and generating AICD, a cleavage product of APP that may interact with the RAP1/TET3 complex. APP mRNA levels will be measured by RT-qPCR. Increased APP expression would suggest activation of γ-secretase and elevated nuclear AICD.

1b. Examine RAP1 transport: Previous studies showed reduced nuclear RAP1 and increased cytoplasmic RAP1 under oxidative stress, suggesting nuclear export. RAP1 trafficking will be evaluated using (1) leptomycin B (LMB), a CRM1-dependent nuclear export inhibitor, and (2) a RAP1 mutant (I312R) that cannot enter the nucleus. Following LMB treatment, RAP1 localization will be assessed by cell fractionation and immunoblotting under normal and serum-free conditions. Increased nuclear RAP1 in serum-free/LMB-treated cells would support RAP1 shuttling during oxidative stress. Separately, glioblastoma cells will be transiently transfected with RAP1-I312R under serum-free conditions, and RAP1 and Aβ levels will be quantified by immunoblotting and ELISA. Reduced Aβ levels would implicate AICD in Aβ production.

1c. Test additional oxidative stressors: Cells will be treated with H_2O_2 or tert-butyl hydroperoxide (tBHP) to induce oxidative stress. Conditions will be optimized and verified using CellROX staining. Once established, experiments described in Aims 1a and 1b will be repeated.

1d. Assess RAP1 and PS1 localization: Immunofluorescence will be performed using RAP1 and PS1 (or other γ-secretase subunit) antibodies to compare protein distribution and signal intensity between control and oxidatively stressed cells.

Aim 2: Identify RAP1 and TET3 target genes that may influence Aβ production

Gene expression studies will be conducted in SH-SY5Y and U251 cells. Following primer validation, RT-qPCR will compare expression of candidate genes in control, serum-deprived, H_2O_2-treated, and tBHP-treated cells. We will also examine NeuroD1, a validated TET3 target implicated in neural stem cell regulation through the JAK2-STAT3 pathway. These studies will determine how oxidative stress alters gene expression and may reveal new transcriptional functions of RAP1 relevant to Aβ peptide production.

Proposed One-Year and Long-Term Outcomes:

This proposal investigates the link between the telomere-protective protein **RAP1** and Alzheimer's disease–related pathways, focusing on its potential roles in neurodegeneration and gene regulation. The project will also provide training opportunities for two technicians and two student researchers in Alzheimer's disease research. The anticipated outcome is a peer-reviewed manuscript to be submitted by the end of the fiscal year.

Year End Progress Summary:

***Specific aim 1*. Investigate the relationship between oxidative conditions and amyloid peptide production**.

1a. Measure γ-secretase activity. To investigate γ-secretase activity under oxidative stress, U251 cells cultured under normal and serum-starved conditions were subjected to cellular fractionation, and AICD levels were analyzed by immunoblotting. Unexpectedly, AICD levels were enriched in the cytoplasmic fraction rather than the nuclear fraction, suggesting that oxidative stress may alter AICD localization or intracellular trafficking. To further assess the relationship

between oxidative stress and APP processing, primer sets for APP are currently being validated for quantitative RT-PCR analysis of APP mRNA expression. These studies will help determine whether serum starvation influences APP transcription and γ-secretase-mediated cleavage.

1b. Functional Analysis of RAP1 Mutants: To investigate the role of RAP1 in Aβ peptide production, two human RAP1 mutants, I312R and F336R, were generated. These amino acid substitutions disrupt the interaction between RAP1 and TERF2. Wild-type and mutant RAP1 alleles were cloned into a CMV-driven mammalian expression vector containing a FLAG epitope tag and transiently transfected into U251 glioblastoma cells. Successful overexpression was confirmed by immunoblotting. Cellular fractionation coupled with immunoblot analysis demonstrated that overexpression of both wild-type and mutant RAP1 resulted in increased cytoplasmic RAP1 levels, while nuclear RAP1 levels remained largely unchanged. Immunofluorescence microscopy yielded consistent results, confirming preferential accumulation of the overexpressed proteins in the cytoplasm. To determine the effect of RAP1 on amyloidogenic processing, Aβ peptide levels in conditioned media were quantified by enzyme-linked immunosorbent assay (ELISA). Overexpression of wild-type RAP1 significantly increased Aβ production. Notably, both RAP1 mutants produced a comparable increase in Aβ peptide levels despite their inability to interact with TERF2. These findings suggest that RAP1 directly influences γ-secretase-mediated Aβ production through a mechanism that is independent of TERF2-associated telomeric and transcriptional functions.

1c. Evaluation of Oxidative Stress Inducers: To identify suitable conditions for inducing oxidative stress (OS), U251 and SH-SY5Y cells were independently treated with a range of hydrogen peroxide (H_2O_2) and tert-butyl hydroperoxide (tBHP) concentrations for varying incubation periods. The extent of oxidative stress was assessed using CellROX staining followed by immunofluorescence microscopy. Although both agents effectively induced oxidative stress, they also caused substantial cytotoxicity and deterioration of cellular morphology. Consequently, serum starvation was selected as the preferred method for inducing oxidative stress in subsequent experiments because it produced a more controlled and physiologically relevant stress response while preserving cell integrity.

1d. Immunofluorescence Analysis of RAP1 and PS1: Immunofluorescence studies were performed in SH-SY5Y cells to examine the subcellular localization of RAP1 and presenilin-1 (PS1), a core component of the γ-secretase complex. Localization patterns of endogenous RAP1 and FLAG-tagged RAP1 were analyzed both independently and in combination with PS1 staining. After evaluating multiple PS1 antibody preparations, reproducible co-localization of RAP1 and PS1 was observed predominantly within the cytoplasm. RAP1 staining intensity was consistently greater than that of PS1. Furthermore, FLAG-tagged RAP1 exhibited enhanced cytoplasmic accumulation under both standard and serum-starved conditions, supporting a potential functional association between cytoplasmic RAP1 and the γ-secretase complex.

Aim 2: Identify RAP1 and TET3 target genes that may influence Aβ production: A total of 16 candidate genes were evaluated for expression in U251 glioblastoma cells, including seven TET3 target genes, three REST target genes, and six RAP1 target genes. Several primer sets required redesign and optimization to achieve reliable amplification and specificity. Gene expression profiles were compared among cells maintained under normal conditions, serum-starved cells, and cells exposed to H_2O_2-induced oxidative stress. These analyses revealed distinct and potentially biologically significant transcriptional changes in response to oxidative stress. Notably, four genes exhibited approximately 10-fold increases in expression relative to control cells. Based on these results, subsequent studies will focus on these high-priority targets. To determine whether regulation is mediated directly by RAP1, TET3, or associated transcriptional complexes, chromatin immunoprecipitation (ChIP) assays will be performed to assess protein occupancy at corresponding gene regulatory regions. This approach provides mechanistic insight.

Work presented at the **ASBMB 2026 Annual Meeting March 7 – 10, 2026**. National Harbor, MD.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Studies on Kv6.1 silent subunit expression and function in hippocampal neurons during Alzheimer's disease. Joao Carvalho-de-Souza, DVM, PhD and Layla Al-Nakkash, PhD. Department of Physiology, Midwestern University; Arizona Alzheimer's Consortium.

Specific Aims:

SA-1: To determine the transcription levels of *Kcng1* gene and the expression of their product Kv6.1 subunit in hippocampi from 3xTg-AD mice. These tests will demonstrate the levels of *Kcng1* transcripts in the hippocampus from 3xTg-AD mice in comparison with that from their genetic background C57BL6/129 mix (C57) mice. This hypothesis stems from the findings in humans suggesting *KCNG1* gene transcription levels are associated with AD. 3xTg-AD mice are a well characterized mice strain that displays AD pathology including the referred hyperexcitability of the hippocampal neurons. All mice to be utilized will be of both sexes for potential sexual dimorphism considerations. Transcription levels of *Kcng1* will be evaluated by RT-PCR method. For comparing purposes, we will study the transcription of other genes encoding other Kv subunits that are functionally related to Kv6.1 subunits and that are knowingly transcribed in the hippocampal formation. These genes/Kv subunits are *Kcnb1/Kv2.1*, *Kcnf1/Kv5.1*, *Kcng3/Kv6.3*, *Kcnv2/Kv8.2, Kcns2/Kv9.2*, and *Kcns3/Kv9.3*. In addition, we will study the levels of the protein Kv6.1 subunit (encoded by *Kcng1* gene) in hippocampal tissues using western blotting (WB). These experiments will serve to determine the putative correlation between the expression of *Kcng1* gene and AD to pave the way for new lines of investigations upstream and downstream the expression of this gene in the context of AD.

SA-2: To study the role of Kv6.1 potassium channel subunit in the neuronal hyperexcitability of hippocampal neurons in 3xTg-AD mice. We will isolate and culture neurons from 3xTg-AD mice hippocampi for neuronal excitability studies. Our results will be compared to those from our control C57 mice, and we will utilize males and females from both mice strains for sexual dimorphism considerations. Using whole-cell patch clamp, current clamp, we will evaluate hippocampal neurons excitability differences between those from 3xTg-AD and C57 mice. We will analyze the threshold for action potential generation, action potential firing rate frequency, and action potential features that indicate the role of a specific potassium channel when possible. These features will be action potential duration, decay time and decay time derivative. Next, we will seek to pinpoint the amplitude of the currents mediated by potassium channels containing Kv6.1 subunits. These experiments will be done with the neuronal membranes under voltage clamp using whole cell patch clamp. In both current clamp and voltage clamp experiments, we will use the blockers RY785 and stromatoxin-1 (ScTx1) that in combination serve to isolate the currents mediated by heteromeric Kv channels to reveal their roles in each type of experiment.

Background and Significance:

Alzheimer's disease (AD) is a progressive neurodegenerative brain disease that affects memory, thinking and behavior in humans, and it is the most common cause of cognitive impairment. The rising impact of AD is a growing public health crisis in Arizona. Early symptoms of AD include lack of recent memory, while late stages of the disease may include severe memory loss, severe cognitive decline and functional impairment.

The exact cause of AD is unknown, but genetics, environment, lifestyles, and age play a role. Living patients and preclinical models have shown hippocampal neurons hyperexcitability as a common sign in the initial stages of AD. It is plausible to believe the hyperexcitability of these neurons is related to the symptoms of AD. The exact causative mechanisms of hyperexcitability are unknown, but ion channels certainly play a role in this regard.

A recent GWAS with over 430,000 underrepresented multi-ancestry individuals found *KCNG1* gene, which encodes for a voltage-gated potassium (Kv) channel subunit Kv6.1, in association with AD by a minimum allele frequency (MAF) of 0.2908. We reason that this variant locus regulates *KCNG1* gene expression, and therefore the abundance of the Kv6.1 subunit in the membranes of hippocampal neurons, to increase their excitability and take part in AD symptoms. The purpose of this study is to collect high-quality scientific data to identify Kv6.1 subunit as a modulator of hippocampal neuron excitability, with an important role during AD pathogenesis.

The hereby proposed study of the *KCNG1* gene expression and the function of its product Kv6.1 subunit in the excitability of hippocampal neurons is crucial to understand the relation between *KCNG1* gene and AD. Here we aim at comparing the hippocampus from 3xTg-AD mice with those from C57BL/6-129 mix (genetic background controls) mice in regards to: *i*) *Kcng1* gene transcription levels, *ii*) Kv6.1 subunit total protein level, and *iii*) neuronal excitability and heteromeric Kv channel-mediated potassium currents. We will address potential sexual dimorphisms.

Preliminary Data, Experimental Design and Methods:

We have previously studied potassium channels, including silent Kv subunits, with respect to gene transcription and protein expression. Our studies in the protein level are focused on their function (ion channels studies using electrophysiology), but we are also experience in detecting protein levels by immunolabelling followed by fluorescence detection, aka immunofluorescence. Transcription levels are studied using mRNA extraction and purification from hippocampal tissues. Next, purified mRNA is used to synthesize cDNA, proportionally and indiscriminately. Lastly, certain genes represented in the cDNA pool such as *Kcng1*, mainly, and many others for comparison and rationalization will be selectively amplified by qPCR. Data is acquired in duplicates, from multiple tissues derived from the two mice strains of both sexes each. For protein detection hippocampal tissues from both mice strains, both sexes, will be collected, sliced and prepared for immunolabeling for the detection of protein targets such as Kv6.1 subunit, mainly, and many others for comparison and rationalization using fluorescence microscopy. Kv6.1 subunits will also be functionally detected in hippocampal neurons from both mice strains, both sexes, as part of heteromeric ion channels formed by Kv6.1 and Kv2.1 subunits. Electrophysiological detection in this case will be paired with transcriptional and immunofluorescence data since there is no pharmacology available for Kv6.1-containing ion channels.

Proposed One-Year and Long-Term Outcomes:

Our analytical and detailed method provides for the study of specific Kv channels (e.g., heteromeric Kv2.1/Kv6.1 channels) on hippocampal neurons from male and female 3xTg-AD and C57 mice.

The data collected with the present proposal will enlighten the pathology of AD with a new druggable target to treat the disease's symptoms. For the first time a protein relating to an ion channel, Kv6.1 subunit, has been associated with the disease in humans in a multi-ancestry study. The association was found strong, with a MAF=0.29. Based on those findings by others, we propose a straightforward study to address Kcng1 transcription and its product Kv6.1 expression in the cell membrane and function. The end goal is to determine the role of Kv6.1 subunit in the excitability of neurons from the EC and the hippocampus that are the areas of interest in the brains with respect to AD pathology. Our data will have the potential to delineate a path to describe important questions such as the reason neurons malfunction and/or die in the EC and the hippocampus area in response to the expression of Kv6.1. We believe this study will enable the collection of high-quality data that will serve as the basis for externally funded research in our labs. We aim at an R-series proposal with the NIH such as FOAs PA-25-246 (Small Research Grant Program for the Next Generation of Researchers in AD/ADRD Research (R03

Clinical Trial Optional)) and/or PAR-25-332 (Research on Current Topics in Alzheimer's Disease and Its Related Dementias (R01 Clinical Trial Optional)).

Year End Progress Summary:

We are currently processing tissues from relatively aged C57BL/6 and C57BL/6;129 mix-strain mice. Students and the technical body of the group are currently under training for tissue collection and processing. Considerable relative delays before actual consistent data becomes available for group analysis are mainly due to time available to train the technical body (research assistant) and students. Untrained personnel would ineffectively utilize our limited resources, making the purpose of this project initiative less competitive. A contribution to the current relative delay stemmed from approval protocols to use animals and the facilities. We are currently optimizing tissue extraction for RNA extraction (for PCR quantifications) and for histology/immunofluorescence (for protein quantifications). Cell culture, for electrophysiology, is in the final steps to become active, then student training will follow before the electrophysiological data (pertaining to Kv6.1 expression in hippocampal neurons) become available.

After multiple rounds of data collections and rationalization, we envision grant applications to state agencies such as ABRC, foundation grantors such as BrightFocus, and national sponsors such as the NIH. With the limited resources provided by the AAC and with the help of MWU (through personnel, students, and PI time), we intend to develop this topic to such a level that we will become eligible to apply for research dollars. As time is key and utterly necessary, in the best-case scenario , we envision sending out applications within the next calendar year. Lastly, our data collection may generate publishable data. The genetic data, because of its novelty, can serve to set the stage for the establishment of our 3xtg-AD mice model as one that will have a signature target protein (Kv6.1 subunits) as a major and determinant player in experimental AD. In this regard, we are currently talking with Dr. Paulo Pires, from the University of Arizona COM-T, about efforts to apply our rationale and approach to a different model that he uses in his lab for his research on cerebral circulation and cognition: 5x-FAD mice. We plan to compare our models in a publication about ion channel transcription in AD mice models and their genetic backgrounds.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

The Opening Minds through Art Program with Unhoused Older Adults: An Implementation Pilot Study. Tiffany Hughes, PhD, MPH, MBA, FGSA, Alison De la Montaigne, EdD, OTR/L, Risa Mechola, PhD, ABPP(CN), Stephanie Christensen, PhD, CCC-SLP, Patrice Ayala, DPT. Midwestern University; Arizona Alzheimer's Consortium.

Specific Aims:

Aim 1: Using implementation science methods, study the use of the evidence-based OMA program with unhoused older adults residing at The Senior Haven. The OMA program is widely replicated and has been shown to benefit older adults living with dementia in the community and in institutions such as assisted living, memory care, and skilled nursing. The focus of this aim will be to examine the necessary preconditions for implementing the OMA program in a permanent supportive housing setting for older adults.

Aim 2: Explore the potential effects of the OMA program on unhoused older adult's cognitive functioning, physical health, affective and emotional well-being, social and everyday functioning, and quality of life. Art therapy has been shown to benefit older adults living with dementia and unhoused individuals, separately, but not unhoused older adults with cognitive impairment or possible dementia. Hypothesis: Older adults residing at The Senior Haven and participating in the OMA program will experience benefits to their cognitive functioning and other health and quality of life outcomes.

Aim 3: Explore the impact of the OMA program on health care students' preparedness for caring for older adults with cognitive impairment and dementia. Reports indicate that many health care professionals are not confident in their ability to care for people with dementia or mild cognitive impairment (MCI), and that there are gaps in training students to work with the geriatric and dementia/MCI populations in the future. Hypothesis: Students who participate in the OMA program as part of an interprofessional course, compared to control students, will be better prepared to work with older adults and those with dementia as part of an interprofessional team.

Background and Significance:

Two important public health issues are converging with the aging of the population – dementia and homelessness, that require novel interventions and enhanced health care training to minimize their future impact. Currently, there is no cure for any type of dementia, only medications that might slow the progression of cognitive decline and treat the behavioral symptoms (Breijyeh & Karaman, 2020). Therefore, maintaining independence and quality of life as well as a sense of purpose are important for those living with dementia.

The Opening Minds through Art (OMA) program was developed at Miami University Scripps Gerontology Institute in2007 as a standardized expressive art-based program grounded in person-centered care principles (https://scrippsoma.org/). The OMA program is designed to be intergenerational with student volunteers paired with older adults living with dementia (artists). Through step-by-step intentional artmaking, OMA provides students with immersive learning experiences that challenge stereotypes and foster empathy beyond traditional classroom learning. Art therapy is a valuable non-pharmacological intervention for people with dementia as it provides cognitive stimulation, emotional expression, and social interaction with the potential to delay institutionalization and enhance quality of life (Deshmukh et al., 2018). Similar benefits may apply to the unhoused where, according to the American Art Therapy Association (AATA; https://arttherapy.org), art therapy allows them "to explore their feelings, reconcile emotional conflicts, foster self-awareness, manage behavior, develop social skills, improve reality orientation, [and] reduce anxiety and increase self-esteem." The impact of art therapy on older

adults with dementia or cognitive impairment and who are unhoused has not been studied. The OMA program is ideally suited to fill this research gap.

The rising number of older adults living with dementia who are unhoused poses a significant threat to the public health and health care systems, necessitating both (1) therapies that can improve health and social outcomes for this population and (2) professionals who have the confidence to care for this population from an interdisciplinary and public health perspective. OMA is an evidence-based program with known positive benefits for older adults living with dementia and for training outcomes in geriatrics and dementia. The significance of this proposed work is to study how OMA can be implemented with a new population to expand its reach and to accelerate the translation of research into practice.

Preliminary Data, Experimental Design and Methods:

This grant aims to expand a CHS Research Facilitation grant (award period July 1, 2024-June 30, 2025; PI: Tamara Turner, Co-I: Tiffany Hughes). Through this grant, a 1-credit interdisciplinary course was developed and offered to 17 students from the College of Health Sciences (OT = 8, PT = 2, SLP = 4, Clinical Psychology = 3) in Fall 2024. Students were paired with older adults with a dementia diagnosis who attended a Benevilla Life Enrichment site (adult day center). Through this course offering, we successfully demonstrated that the OMA program can be implemented with Midwestern students through an interdisciplinary course format in partnership with a community organization serving older adults with dementia. Approval was granted by the IRB for a program evaluation of how the experience affected student learning outcomes related to geriatric and dementia care. Our data show that the OMA experience significantly increased student knowledge and positive attitudes about dementia (p-value <0.0001), and specifically increased comfort interacting with people with dementia (p-value <0.001). The results also suggest that after the OMA experience, compared to before, students felt more prepared to work with people with dementia and had reduced negatives stereotypes, prejudices, and discrimination towards older adults. We are currently analyzing qualitative data from student journals, discussion posts, reflection papers, and the end-of-course focus group to better capture the benefits of the program on students' training in geriatric and dementia care.

OMA Intervention and Outcome Assessments: Over the course of the 10-week term, we will conduct activities each week. We plan to repeat this during Fall 2025 and Spring 2026 terms with up to 10 dyads per term. All artmaking sessions will be run by two OMA-trained facilitators.

Aim 1: Using implementation science methods, study the use of the evidence-based OMA program with unhoused older adults with cognitive impairment residing at The Senior Haven.

Participants: Data on the outcome measures listed below will come from different levels of analysis including CASS leadership or Midwestern University CHS leadership (organization), The Senior Haven staff or Midwestern University faculty/staff (individual provider), and CASS clients or Midwestern students (individual consumer).

Aim 2: Explore the potential effects of the OMA program on unhoused older adult's cognitive functioning, physical health, affective and emotional well-being, social and everyday functioning, and quality of life.

Participants: Participants will be older adults currently residing at The Senior Haven, which is a newly opened shelter operated by the Central Arizona Shelter Services (CASS) specifically for older adults aged 55 years and older. The Senior Haven can provide permanent supportive housing for up to 170 clients with an average length of stay of 90 days. Most clients are new to homelessness, although a few are considered chronically homeless, and more medically complex (personal communication with CASS Program Manager Johanna Jorgenson, MSW).

Aim 3: Explore the impact of the OMA program on health care students' preparedness for caring for older adults with cognitive impairment and dementia.

Participants: Current Midwestern University students in the College of Health Sciences programs in Occupational Therapy, Physical Therapy, Speech-Language Pathology, and Clinical Psychology. OMA Volunteers (n ~ 20). OMA volunteers will be students enrolled in the 1-credit elective course offered by the respective program focused on dementia care. Student control group (n ~ 20). Students enrolled in other courses in the participating programs during the same term will be invited to complete the pre- and post-OMA experience measures (except activities specific to the course and the focus group).

Proposed One-Year and Long-Term Outcomes:

We expect this work to result in one manuscript submission in a peer-reviewed publication. We anticipate continued student involvement in this research, which would lead to a Kenneth A. Suarez research day presentation in Spring 2026 at Midwestern. We also intend to submit this work for presentation at the Arizona Alzheimer's Consortium annual scientific meeting in Fall 2026, and at one national conference such as The Gerontological Society of America in Fall 2026 (abstracts due March 2026). The goal of this work is to expand the OMA program's reach across the Valley by serving as a hub for training facilitators working with different populations who would benefit from OMA (personal correspondence with OMA leadership), and to partner with other Universities, such as ASU, to engage more student volunteers. We plan to apply for external funding directly through the Arizona Alzheimer's Consortium to support these plans.

Year End Progress Summary:

Sufficient study participants and control individuals were successfully recruited at The Senior Haven. Student and professional OMA facilitators were successfully trained prior to beginning weekly sessions with study participants. The 10 weeks of planned activities were completed and then duplicated in another academic quarter. Outcome measures were recorded as intended and are being analyzed by study personnel for publication and future grant applications.

Study participants (artists) were supported in presenting their art to others at various venues and the work of the study was featured in a 12news live episode called "Sponsored: Healing through art: Creativity at The Haven"
https://urldefense.com/v3/__https:/www.12news.com/video/entertainment/television/programs/arizona-midday/sponsored-healing-through-art-creativity-at-the-haven-midwestern-university-cass-central-arizona-shelter-services/75-249279e9-82cf-4aa2-a0a0-244c4c4cf58e__;!!J-3uQMwJ!PeSf5dugScdfh9Lbgb9C440x9y8H0xuLnRyCao9PLgUgiJ6Am9LvK6iWQYSFnboZX4TogVx7F3dE_UjImmi3y8Y$

This study was successful in meeting its goals even though one of the investigators changed job responsibilities midway through the grant term and there was also a change of technical staff when that staff member left the university. These roles were subsequently filled by another investigator and students who had undergone OMA facilitation training. Despite these challenges, the data was successfully collected, and data analysis is being completed. We are planning to write up and publish the work and will use the data for future grant applications to organizations that support art therapy for seniors and those with cognitive decline.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Elucidating a mechanistic link between progranulin & lysosomal function in Alzheimer Disease. Elizabeth Hull, PhD & Kathryn Leyva PhD. Biomedical Science Program & Department of Microbiology and Immunology, College of Graduate Studies, Midwestern University; Arizona Alzheimer's Consortium.

Specific Aims:

Aim 1: Assay lysosomal protease activity in microglial & neuronal cell lines and primary cultures

Aim 2: Identify PGRN and CTSL mRNA splice variants in response to cytokine treatment

Background and Significance:

PGRN is a pleiotropic signaling molecule. Proteolytic processing of PGRN generates a variety of GRNs which have independent and even antagonistic biological activity. PGRN has characterized roles in regulation of inflammation, growth, lysosomal function, and multiple modes of neuroprotection have been independently identified in disease states. Thus, harnessing the therapeutic potential of PGRN requires elucidation of PGRN processing and how processed PGRN affects lysosomal function. Stabilization of the lysosome-PGRN axis to reduce microglial-mediated inflammation offers a targeted approach to reduce the pathological neuroinflammation associated with early-stage AD. The goal of this work is to explore the mechanisms that establish the lysosome-PGRN axis and characterize its disruption in AD and to determine effective approaches to restoring the lysosome-PGRN axis to prevent neuroinflammation in the development of AD. As lysosomal dysfunction has independent roles in shifting metabolism and promoting inflammation and PGRN is showing promise as a biologic in mouse models, detailing the mechanistic links to rebalance the lysosome-PGRN axis in AD is critically important in the development of new targeted therapeutics for early intervention. As processed PGRN appears to play a role in promoting lysosomal function, if the requisite PGRN processing can be identified, supplementation by a GRN product after appropriate processing may restore lysosomal function, rebalancing the lysosome-PGRN axis to abrogate an inflammatory response.

The work proposed here involves the lysosomal roles of PGRN processing, as defective lysosomal function is linked to neurodegenerative diseases. It is known that PGRN supports lysosomal function in a number of ways, including the trafficking of lysosomal proteases such as prosaposin to the lysosome. In addition, not only is PGRN cleaved by lysosomal proteases but the resultant granulin units bind to and stabilize lysosomal proteases. Reductions in PGRN levels in FTLD and NCL appear to be correlated with lysosomal dysfunction and altered lysosomal processing of PGRN. Additionally, changes in cathepsin L processing are associated with dysfunctional lysosomes. Therefore, the premise of this work is that an inflammatory response shifts both the cell types that produce and the expression of the proteases, such as cathepsin L (CTSL), that process PGRN to GRNs. We hypothesize that the activity of PGRN/GRNs produced during an inflammatory response is responsible for the role PGRN/GRNs play in the inflammatory response linked to pathology in AD. The central question investigated by this proposal is the proposed causal link between inflammation and lysosomal processing of PGRN. Direct mechanisms of lysosomal dysfunction due to PGRN loss have been established but no studies to date have demonstrated a functional link between PGRN processing and lysosomal protease activity, a key determinant of lysosomal function.

Preliminary Data, Experimental Design and Methods:
Preliminary data using the HMC3 human microglial cell line showed that treatment with IFNγ increased, and a cocktail of anti-inflammatory cytokines decreased, IL1β levels, suggestive of altered levels of M1-polarization, respectively. Treatment with PGRN under the same conditions also increases IL1β levels consistent with pro-inflammatory activity. In addition, compromising lysosomal function, either by the addition of hydroxychloroquine or leupeptin treatment, also increases IL1β levels, a finding which reinforces the link between lysosomal dysfunction and inflammation.

We will be using a human microglial cell line (HMC3), a mouse microglial cell line (Sim-A9), a human neuroblastoma cell line (SH-SY5Y), and a mouse neuronal cell line (Neuro2a). Mouse microglial and neuronal primary cells will be used to verify results obtained using cell lines and will serve as a foundation for future experiments using ex vivo brain slice cultures. Based on previous work, 25 ng/mL of IFNγ to polarize microglia to the M1 phenotype and a cocktail of 20 ng/mL IL-4, 20 ng/mL IL-10, and 10 ng/mL each of TGF-β1 and TGF-β2 to polarize microglia to the M2 phenotype will be used. RNA will be isolated from each cell line and PCR performed using specific progranulin (GRN) or cathepsin L (CTSL) primers, including primers that span splice junctions, will be used to identify splice variants. Lysosomal protease activity will be assessed using commercially available FRET peptides specific for detecting cathepsin L and D activity.

Proposed One-Year and Long-Term Outcomes:
We expect cytokine treatments to generate changes in expression of mRNA variants encoding PGRN or CTSL, and resultant changes in lysosomal activity in both cell lines and primary cultures. These experiments will determine whether shifts in PGRN/GRNs, cytokines, and lysosomal function are in direct response to an initial pro-inflammatory or anti-inflammatory challenge. In addition, as lysosomal dysfunction appears to promote inflammation, results are expected to provide a direct assessment of this effect. Comparing results from between cell lines and primary cultures will validate results that may translate to future work using ex vivo cultures.

We anticipate drafting a manuscript based on the above preliminary results and the experiments proposed here. In addition, we will utilize the results generated by these specific aims to continue to seek extramural funding. Specifically, we anticipate that a revision of the NIH REAP grant submitted in February 2024 will be needed prior to funding, and we plan to include data generated by the experiments proposed here in a revised submission to the NIH.

Year End Progress Summary:
Specific progress and ongoing experiments are summarized below by specific aim.

Aim 1: Assay lysosomal protease activity in microglial & neuronal cell lines and primary cultures

HMC3 microglial and SH-SY5Y human neuroblastoma cells were treated with pro-inflammatory or anti-inflammatory cytokines and assessed for cathepsin L (CTSL) activity using a fluorometric assay kit. Overall, cathepsin L activity was higher in the HMC3 microglial cell line compared to the SH-SY5Y neuronal cell line. For HMC3 cells, treatment with a pro-inflammatory (M1) cytokine resulted in higher CTSL activity compared to control. For SH-SY5Y cells, treatment with anti-inflammatory (M2) cytokines resulted in higher CTSL activity compared to untreated and M1-treated cells. We saw higher levels CTSL protein using immunoblot in AD brain tissue vs tissue from normal brains. Initial work has begun using these same cell lines and treatments to assess cathepsin D (CTSD) activity.

We repeated the same experiments using a mouse microglial (Sim-A9) and mouse neuronal (Neuro-2a) cell line. Interestingly, we saw no change in CTSL activity, compared to control, regardless of cytokine treatment; CTSL activity was relatively low as well. However, Neuro-2a cells had significantly higher levels of CTSL activity when treated with pro-inflammatory (M1) vs anti-inflammatory (M2) cytokines, with both cytokine treatments stimulating increased CTSL activity compared to control. For CTSD, we found no differences in CTSD activity in Sim-A9 neuronal cells, but we saw significantly higher CTSD activity in Neuro-2a cells compared to control and M1-treated cells. Ongoing work comparing CTSL activity using Neuro-2a cells with and without neural differentiation may reveal important neuron-specific changes. More work is needed to determine the effect treatment has on GRN production and if treatment (pre- or post-treatment) with PGRN will abrogate these results.

Aim 2: Identify PGRN and CTSL mRNA splice variants in response to cytokine treatment

For HMC3 cells, cytokine treatment resulted in differences in CTSL mRNA variants detected using gel electrophoresis. Treatment with anti-inflammatory cytokines resulted in only 1-22 CTSL mRNAs being detected vs 5-6 CTSL mRNAs from untreated cells. Treatment with a pro-inflammatory cytokine yielded 7-8 CTSL mRNA variants, with only 2-3 that appear to be same/similar band. For SH-SY5Y cells, fewer CTSL variants (3-4) were observed on gel electrophoresis regardless of cytokine treatment, with only 1 visible band for a single CTSL variant when cells were treated with anti-inflammatory cytokines.

Initial attempts at sequencing each mRNA variant from human cell lines were unsuccessful, so will need to be repeated to determine specific differences in the sequences. We are currently working to identify if any mRNA splice variants are found in untreated vs. cytokine treated mouse cell lines.

FY 25-26 Extramural Grant Applications Funded during Reporting Period

Elizabeth Hull & Kathryn Leyva **Midwestern Arizona Alzheimer Consortium** Elucidating a mechanistic link between progranulin & lysosomal function in Alzheimer Disease	$9,912 Funded 7/1/25-9/30/26
Elizabeth Hull & Kathryn Leyva **Arizona Alzheimer Consortium** Non-coding RNA regulation of the progranulin gene during the inflammatory response in Alzheimer Disease	$30,000 Funded 7/1/25-6/30/26

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Non-coding RNA regulation of the progranulin gene during the inflammatory response in Alzheimer Disease. Elizabeth Hull, PhD & Kathryn Leyva PhD. Biomedical Science Program & Department of Microbiology and Immunology, College of Graduate Studies, Midwestern University; Arizona Alzheimer's Consortium.

Specific Aims:

Aim 1: Assay targeting of the 3' UTR of GRN and related genes in inflammation

Aim 2: Correlate ncRNA and mRNA in AD samples

Background and Significance:

The link between the number of functional copies of the GRN gene and neurodegenerative disease is supported by many studies. As haploinsufficiency is rare, this relationship between GRN gene dose and neurodegenerative disease suggests that the level of PGRN protein production is key to disease processes and supported by the link between cognition during healthy aging. However, the timing and source of PGRN expression appears to be key to its therapeutic benefit. PGRN production is differentially controlled in M1 and M2 polarized microglia; with immune challenge, PGRN stimulates astrocyte and microglial activation to promote neuroinflammatory reactions and in GRN+/- mice, neuroinflammation appears to be separate from neuronal deficits. As these data suggest that the cell type and timing in which PGRN production appears impacts disease processes, this work focuses on defining differences in PGRN production in microglia and neurons, both key sources of PGRN in the brain. Thus, our goal is to delineate the mechanisms leading to the differential control of PGRN expression in microglia and neurons during the inflammatory response so that PGRN production can be boosted in the cell type which will most impact the AD disease process.

This work is focused on boosting PGRN production by increasing GRN mRNA levels. However, the transcriptional regulation of PGRN production is complex as the GRN promoter has many response elements, and many other factors affect GRN mRNA expression. 830 genes have been identified that either increased or decreased PGRN levels 1.5-fold or more in Neuro2a cells, suggesting that a more targeted approach in understanding GRN mRNA regulation is needed. Thus, our focus is on post-transcriptional regulation of GRN mRNA, as expression of PGRN appears to be affected by the widespread aberrant RNA processing (utilizing alternative splice sites) closely linked to neurodegeneration, as well as by ncRNA regulation of GRN mRNA. One class of ncRNAs, miRNAs, bind to target mRNA strands to negatively regulate mRNA expression. In addition to our focus on GRN mRNA, mRNA for proteins known to affect PGRN mRNA (e.g. TDP-43) will be examined. The significance of disruptions in mRNA processing is demonstrated by the fact that levels of both phospho-Tau and TDP-43 aggregations are associated with disrupted mRNA processing and anti-sense RNA approaches have increased PGRN production in preliminary studies. In addition, the newly FDA-approved drug, inclisiran, which is an anti-sense RNA therapeutic targeting PSK9 to effectively lower LDL cholesterol, supports the efficacy of anti-sense RNA approaches in patients. By identifying mRNA-based approaches that result in increased PGRN expression, this work addresses the gap in knowledge of how *GRN* expression can be positively regulated to reduce neuroinflammation, which may facilitate development of a targeted therapeutic.

Our innovative solution defining how GRN mRNA levels may be boosted through epigenetic approaches is potentially transformative because it will further the pre-clinical development of

early interventions for the treatment of AD. The overall impact of focusing efforts on mechanistic characterization of cell type and inflammation-specific GRN gene expression will delineate the parameters for future epigenetic therapies. Building on the expertise of the lab in educating and involving students in research, this work will prepare the next generation of clinicians while results will further define the role of PGRN in Alzheimer disease.

Preliminary Data, Experimental Design and Methods:

From previous work, we have determined the optimal dosages of cytokines necessary to polarize microglial cells to either the M1 or M2 phenotype, with immunofluorescence confirming expression of HLA-DR (M1) or CD206 (M2). Preliminary data using a luciferase reporter construct, containing the 3' UTR of GRN or TARDBP, have shown that inflammatory cytokines, specifically IFNγ, affect mRNA regulation as assessed by alterations in luciferase signal compared to control.

Methods for Aim 1: The ability of the inflammatory response to alter GRN expression via 3' UTR targeting will be established using reporter constructs transfected into microglial and neuronal cell lines. This regulation will then be detailed by 1) capturing and quantitating GRN mRNA binding proteins (including TDP-43) by affinity and mass spectrometry methods and 2) measurement of GRN-targeting ncRNAs known to be altered in AD progression by qPCR during the immune response. Results will be confirmed in primary cultures.

Methods for Aim 2: The full spectrum of RNA in primary cultures and AD patient samples will be analyzed by RNA sequencing and non-coding RNA (ncRNA) arrays using processing to preserve the ncRNA that are frequently lost in routine RNA analyses. Initial work will focus on those miRNAs identified in the literature as changing in AD (Table 1) but will include the most altered ncRNAs identified in the ncRNA arrays. The expression of ncRNA will be correlated to RNA targets, and contributions of neurons and microglia under different inflammatory conditions will be identified. In addition, prediction tools (e.g. miRTarBase and miRDB) will be used to identify additional mRNA targets and the impact of each ncRNA on multiple target mRNAs assessed. When warranted, data will be verified experimentally by additional experiments after treatment with RNA mimics and inhibitors.

Proposed One-Year and Long-Term Outcomes:

Data generated in Aim 1 will 1) identify the most changed ncRNAs in response to inflammatory cytokine signals in microglia and neurons, 2) establish potential crosstalk between ncRNA targeting of the 3' UTR of GRN, TARDBP, and SORT1 as both TDP-43 and sortilin have been shown to affect PGRN levels, and 3) assess the involvement of proteins in 3' UTR regulation. In aggregate, these data will define ncRNA targets for future therapeutics by delineating their cell type and inflammation specific roles. Data generated in Aim 2 will 1) establish the cell type and inflammation specific contributions to changes in the ncRNA profile in patient samples, thereby determining if cell type and inflammation specific signatures can be detected in patient samples, and 2) have the potential to provide data on other ncRNAs, particularly the long non-coding RNAs shown to be associated with AD. As the source and timing of PGRN production is key to its therapeutic effects, these analyses may identify a specific cell type or inflammatory pathway to guide the development of future therapeutics.

We anticipate drafting a manuscript based on the above preliminary results and the experiments proposed here. Data generated will be used to bolster a recent submission for funding to the Department of Defense Peer Reviewed Alzheimer's Research Program (PRARP) program and support a parallel application to the NIH.

Year End Progress Summary:
Specific progress and ongoing experiments are summarized below by specific aim.

Aim 1: Assay targeting of the 3' UTR of GRN and related genes in inflammation

Our data show that expression of both the *GRN* and *TARDBP* genes may be significantly altered by miRNA during the inflammatory response. In the SHSY-5Y neuronal cell line, we saw that pro-inflammatory cytokine treatment (IFNγ) significantly increased luciferase activity from the *GRN* reporter construct, suggesting an increase in *GRN* expression. Interestingly, the effect of *GRN* 3'UTR regulation is abolished with the rs5848 polymorphism reporter construct, which contains a mutation in the miR-659-3p binding site within the 3' UTR, suggesting a potential regulatory role of this miRNA for the *GRN* gene. In the same neuronal line, *TARDBP* appeared to show an opposite effect; IFNγ resulted in significantly decreased luciferase activity from the *TARDBP* 3' UTR reporter construct, suggesting a decrease in *TARDBP* expression. Ongoing experiments are comparing the regulation in SHSY-5Y cells with and without neuronal differentiation. In the HMC3 human microglial cell line, cytokines do not appear to alter luciferase expression, suggesting no change in 3'UTR targeting of either *GRN* or *TARDBP.*

Aim 2: Correlate ncRNA and mRNA in AD samples

Work on this specific aim is ongoing. We began by performing a miRNA array to assess changes in miRNA expression in HMC3 microglial cells between cells treated with M1 (pro-inflammatory) and M2 (anti-inflammatory) cytokines. Treatment with M2 cytokines increased expression of 11 miRNAs tested, 12 total including miR-659-3p from the luciferase reporter construct data. Ongoing work is focused on three areas: 1. identifying PGRN-targeting miRNAs altered by the inflammatory response in both neuronal and microglial lines, 2. testing the ability of altered miRNA levels to restore lysosomal function and alter inflammation, and 3. Obtaining AD samples to perform comparative ncRNA and mRNA arrays.

FY 25-26 Extramural Grant Applications Funded during Reporting Period

Elizabeth Hull & Kathryn Leyva **Midwestern Arizona Alzheimer Consortium** Elucidating a mechanistic link between progranulin & lysosomal function in Alzheimer Disease	$9,912 Funded 7/1/25-9/30/26
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ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Investigating the Role of Stress Hormones on Astrocyte Neuroenergetics. Kathryn Lawson, PhD, Kimberly Bussey, PhD, Thu Huynh, PhD. Midwestern University; Arizona Alzheimer's Consortium.

Specific Aims

1. Evaluate the effects of chronic corticosterone exposure on cellular phenotypes in a murine astrocyte cell line model.
2. Investigate the effect of chronic corticosterone exposure on glucose uptake and metabolism in a murine astrocyte cell line model.

Background and Significance:

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by amyloid-β plaques, neurofibrillary tangles, and premature neuronal death, primarily in brain regions critical for memory and executive function. Although genetic factors contribute, AD is a complex disease in which environmental exposures play a significant role in disease manifestation. The brain consumes roughly 20% of the body's glucose to support energy production, neurotransmission, and antioxidant defense. Cerebral glucose uptake is mediated by GLUT1 (primarily expressed on astrocytes) and GLUT3 (primarily expressed on neurons), and the astrocyte-neuron lactate shuttle provides an alternative means of meeting neuronal energy demands. Impaired cerebral glucose metabolism is an established hallmark of AD, and chronic stress represents a plausible environmental contributor to this metabolic disruption. Stress hormones such as corticosterone oppose insulin action and, with prolonged secretion, induce hyperglycemia and insulin resistance. Emerging evidence suggests these effects extend to the central nervous system. Previous studies in primary hippocampal astrocytes have demonstrated that supraphysiological glucocorticoid levels alter glucose uptake, anaerobic glycolysis, and glycogenolysis. Additionally, corticosterone has been shown to modulate amyloid-β synthesis and degradation in astrocytes, suggesting a direct link between stress hormone exposure and AD-related pathology. We hypothesize that both transient and chronic exposure of astrocytes to physiological levels of corticosterone alters cellular phenotypes and glucoregulatory pathways, with potential consequences for neuronal function and AD pathogenesis.

Preliminary Data, Experimental Design and Methods:

Preliminary data from Dr. Huynh's laboratory demonstrated that a 4-week chronic mild stress protocol in adult male mice reduces GLUT1 glucose transporter levels in the hippocampus, while neuronal GLUT3 transporter levels are unchanged. Because GLUT1 is primarily expressed on astrocytes, these findings suggest that chronic stress preferentially disrupts astrocyte-mediated glucose transport. Dr. Bussey's prior studies in a cancer cell model have demonstrated cortisol-dependent changes in single cell RNA expression profiles that persist after cessation of treatment. Together, these data suggest that corticosteroid exposure of neural cells may result in durable changes in gene expression that can alter cellular behavior and metabolism. To test our hypothesis, we proposed to develop a corticosterone-treated cell model of C8-D1A immortalized murine astrocytes. These cells were grown under three conditions: control cells maintained in standard media, corticosterone-treated cells grown in 1000 nM corticosterone for 28 continuous days, and reverted cells exposed to corticosterone for 14 days followed by return to standard media. Under **Specific Aim 1**, we proposed to characterize cellular phenotypes using HoloMonitor live cell imaging (morphology, proliferation, and migration), assess amyloid-β production by ELISA, quantify glucocorticoid-responsive proteins (GR, FKBP5, PLZF) and glucose transporters (GLUT1, GLUT3) by western blot, and visualize GR localization by

immunofluorescence. Under **Specific Aim 2**, we proposed plate-based assays for glucose uptake, lactate production, and ATP levels to evaluate the metabolic consequences of chronic corticosterone exposure.

Proposed One-Year and Long-Term Outcomes:

Completion of the proposed aims would yield a fully characterized corticosterone-exposure model with quantitative data on cellular phenotype, glucocorticoid receptor signaling, amyloid pathway protein expression, Aβ secretion, and metabolic function (glucose uptake, lactate, ATP) across all three treatment conditions. These data, together with data collected under the currently funded Year 2 proposal, would provide the preliminary evidence needed to pursue both intramural and extramural funding through multiple mechanisms. In the 2026-2027 funding cycle, we will apply for a One Health Research Stimulus award to compare signaling profiles between glucocorticoid-treated murine and human astrocytes, which we have recently obtained. An application to the John Templeton Foundation, with Dr. Bussey as Principal Investigator and focused on testing predictions of the atavism theory that would extend the theory to the aging brain, will be initiated with a letter of intent due July 15, 2026. Our long-term goal is to pursue an investigator-initiated R01 application to the NIH, targeted for Spring 2027, to identify mechanisms linking chronic stress to AD-relevant neuroenergetic dysfunction and to facilitate translation into clinical interventions.

Year End Progress Summary:

1. Cell Line Development and Banking. Three C8-D1A murine astrocyte cell lines were successfully established and banked in liquid nitrogen with three biological replicates per condition (control, selected, reverted). Completion of the full replicate set required additional time due to administrative and technical challenges. Establishment of a material transfer agreement between Midwestern University and the cell supplier (Cytion) delayed the start of the protocol until late August 2025. Following receipt of cells, it was necessary to repeat the one-month corticosterone treatment protocol due to cell contamination and technical issues encountered during lysate preparation. These have been resolved. The current triplicate set enables three independent biological replicates for western blot and HoloMonitor analyses, and all lines have been banked in liquid nitrogen at the completion of each treatment protocol. HoloMonitor analyses were initiated on a newly purchased instrument that arrived on campus in May 2025, requiring concurrent optimization of imaging and analysis parameters alongside data collection.

2. Cellular Phenotype (Specific Aim 1). HoloMonitor live-cell imaging revealed that reverted cells proliferate at approximately twice the rate of control and selected cells, which are indistinguishable from one another. Analysis of cell area distributions demonstrates a loss of intercellular morphological heterogeneity in selected and reverted conditions relative to control, indicating that corticosterone-induced phenotypic changes persist following hormone withdrawal. Western blot analysis shows elevated expression of the glucocorticoid-responsive gene FKBP5 in selected cells. Notably, protein levels returned to near-baseline in reverted cells, indicating normalization of canonical GR signaling after corticosterone withdrawal. This normalization contrasts with the persistent proliferative and morphological changes described above, suggesting a dissociation between active receptor signaling and downstream cellular phenotype, and implies epigenetic alterations to gene expression. Western blot analysis of amyloid precursor protein (APP) showed no treatment effect. Neprilysin was not detected under the current lysis conditions and will be re-examined following lysis protocol optimization. Glucocorticoid receptor expression was not altered by corticosterone treatment. Immunofluorescence experiments to characterize GR subcellular localization are planned for this summer.

3. Glucose Uptake and Metabolism (Specific Aim 2). All reagents for glucose uptake, lactate, and ATP quantification (Cayman Chemical) have been purchased and received. Execution of these assays was delayed by concurrent priorities including additional C8-D1A treatment protocols, western blot equipment optimization, and banking of newly received HT-22

hippocampal neurons for the Year 2 funding period. The assays are targeted for completion within the first month of the new fiscal year. Western blot analysis of GLUT1 and GLUT3 did not yield detectable signal under initial conditions. Lysis protocol optimization is underway to improve membrane protein recovery for these targets. We are also designing immunofluorescence experiments to characterize the relative membrane versus cytoplasmic abundance of these transporters.

4. Funding Trajectory and Dissemination. This work has been funded for a second year by the Arizona Alzheimer's Consortium (2026-2027, $14,000). The Year 2 proposal, *Investigating the Impact of Stress Hormone-Induced Astrocyte Changes on Neuronal Function,* extends the model to single-cell RNA sequencing of the three C8-D1A cell lines and examination of the effects of astrocyte-conditioned media on HT-22 murine hippocampal neuron health and function. In the 2026-2027 funding cycle, we will submit a letter of intent to the John Templeton Foundation (Dr. Bussey, PI; due July 15, 2026) and apply for a One Health Research Stimulus award to compare signaling profiles between glucocorticoid-treated murine and human astrocytes, which we have recently obtained. These studies will collectively support an investigator-initiated R01 application to the NIH targeted for Spring 2027. Results from the 2025-26 funding period were presented at the 2025 Kenneth A. Suarez Research Day and will be presented at the Arizona Alzheimer's Consortium Annual Scientific Conference (Tucson, AZ, September 2026).

ARIZONA ALZHEIMER'S CONSORTIUM
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Determination of polymicrobial burden in two postmortem brain regions in AD patients and controls with varying levels of AD-related pathology and cognitive status. Garilyn Jentarra, PhD and T. Bucky Jones, PhD. Midwestern University; Arizona Alzheimer's Consortium.

Specific Aims:

We propose to analyze post-mortem brain tissue from the same subjects in which we previously identified the presence of bacterial DNA using 16S rRNA sequencing. Tissue from two distinct brain regions from four subject groups will be investigated for the presence of fungal species using ITS region long-read amplicon sequencing.

1. Comparative analysis of fungal species based on regions. Fungal DNA will be extracted from two distinct cortical regions differentially affected in AD (superior frontal gyrus and middle temporal gyrus) from each of our subject groups (AD, MCI, HPC, and NDN). Extracted DNA will be sequenced at the Translational Genomics Integrated Microbiomics Center. A comparative analysis of the predominant fungal taxa identified in each brain region will be performed to determine if there are differences in regional susceptibility to fungal infiltration.
2. Comparative analysis of fungal species based on subject group and AD pathology. To accomplish this aim we will compare fungal taxa present in our subjects with impaired cognition (AD, MCI) to those without cognitive decline (HPC, NDN) as determined by scores on the mini mental state examination (MMSE). We will also compare fungal taxa present in subjects with a high degree of AD-related neuropathology (AD, HPC) to those with little to no AD-related pathology (NDN). Samples from patients diagnosed with MCI will not be included in this analysis as the level of pathology present is highly variable. This will allow us to establish whether the distribution of fungal species is associated with cognitive status or linked to the degree of pathology (amyloid plaques and neurofibrillary tangles) present.
3. Determination of cumulative polymicrobial burden and its collective relationship to brain region and AD pathology. Our previously published data from an earlier set of 48 subjects and our preliminary data in this proposal (from a new set of 100 subjects) both show that there are distinct differences in bacterial taxa that are dependent on brain region. Links between pathology and microbial burden were also identified in our published data and will be analyzed in the new data set as well. In this aim we will consider both our fungal data (generated in Aim 1) and our bacterial data (generated from the set of 100 subjects) collectively to determine whether there is region-specific susceptibility to polymicrobial infiltrates (bacteria + fungi) and whether the totality of the microbial burden predisposes to neurodegenerative phenotypes.

Background and Significance:

The central nervous system (CNS) of individuals diagnosed with AD exhibits considerable inflammation, including elevated levels of pro-inflammatory cytokines and morphological evidence of glial activation, suggesting the presence of an immune stimulus chronically in the brain. Further, numerous recently identified gene mutations associated with elevated risk for developing sporadic or late-onset AD (LOAD), affect proteins associated with immune system function, implicating dysregulation of immunity as a potential contributor to AD.

Many reports have identified a wide range of microorganisms in brain tissue in association with AD. These include spirochete type bacteria, HSV-1, and fungi/yeast, including various species of Candida. Recent reports using newer sequencing techniques have added to our understanding of the extent of microbial presence in the brain, not just in AD, but also Parkinson's disease, amyotrophic lateral sclerosis, and multiple sclerosis. The chronic presence of any of these microorganisms in the brain may be sufficient to produce the inflammatory environment present

in AD. Microbial infections can influence both pathology and cognition. Hyperphosphorylation of tau, which drives its aggregation, may be induced by microbial infection. Several recent studies have demonstrated that Aβ functions as an antimicrobial peptide with activity against bacteria, viruses, and fungal species Aβ may therefore be produced in an attempt to limit infection.

We hypothesize that the presence of a specific microorganism may not be as important as a chronic polymicrobial infection and/or the total polymicrobial load (infectious burden). 1) we are analyzing tissues from four groups of subjects associated with a range of AD-associated amyloid and tau pathology and a wide range of cognitive status 2) we are studying two distinct brain regions within the same subjects and; 3) we are studying the cumulative effects of both bacterial and fungal burden. Collectively this study design allows us to evaluate regional susceptibility and the relationship of polymicrobial infection to pathology and cognitive status.

Preliminary Data, Experimental Design and Methods:

We previously published an extensive metagenomic and bacterial component analysis of the bacterial burden found in post-mortem tissue from two different brain regions of the same 48 human subjects. In that study we also found links between bacterial lipopolysaccharide (LPS) levels in the serum of those individuals and cognitive decline. An inverse correlation was identified between brain tissue LPS levels and the presence of the AD-associated vascular pathology known as cerebral amyloid angiopathy (CAA). We validated our sequencing data by demonstrating that brain tissue levels of bacterial LPS (gram-negative) and lipoteichoic acid (LTA, gram-positive) by ELISA aligned closely with the proportions of gram-negative versus gram-positive bacteria identified by sequencing in the same tissue samples.

Because the initial subject groups in that study were relatively small, we subsequently expanded the study to an entirely new group of 100 subjects with 25 individuals in each of the same four subject groups with the goal of verifying the consistency of the regional differences in brain bacterial content identified in the first 48 subjects. For these 100 individuals we have matching SFG and middle temporal gyrus (MTG) tissues for comparison. MTG was chosen instead of ITG in these experiments because not all subjects in this new group had ITG tissue available. However, MTG is the adjoining temporal cortex region and displays similar timing and levels of AD-associated pathology. Since the existence of a brain microbiome potentially associated with pathology is still being established by ourselves and others, we felt that analyzing a completely independent set of subjects was a necessary step to support progress in this area and to increase the power of our study to detect differences between subject groups, as high inter-subject variability has been noted even within subject groups.

This proposal extends our previous analysis to include an evaluation of a likely fungal microbiome in the brain tissue of the same subjects. As described in the Background section, others have described fungi/yeast in AD brain tissue in small numbers of subjects, particularly Candida species. We believe that, at a minimum, Candida species will be identified. Because we are using a sequencing method that is pan-fungal, we have the opportunity to also assess the presence of any other fungal taxa present. With these analyses, we can determine if there are region-specific differences, as seen with the bacterial microbiome. We can also evaluate whether any specific taxa of fungi are associated with either the AD-associated tissue pathology or AD-associated cognitive decline. In addition, we can begin to study potential correlations between the cumulative bacterial and fungal burden of the brain in association with pathology and cognition. Our previous data, while valuable, provides an incomplete picture in the absence of fungal burden data.

Proposed One-Year and Long-Term Outcomes:

We are currently in the process of fully analyzing the bacterial data described in our Preliminary Data section. While waiting for fungal sequencing results, we will complete that analysis so that it can be combined with the fungal data when it is available. We will ultimately publish the collective bacterial and fungal data for this set of subjects as we expect that a more comprehensive description of microbial burden and its association with AD-related pathology will contribute to our understanding of the mechanisms of AD. We will also seek extra-mural funding for the continuation of this work. This will include proposals to the Infectious Diseases Society of America (IDSA) which has been funding explorations of the association between microbes and AD. We also plan to apply for funding for this project from the National Institute of Aging at the NIH, most likely through the R21 mechanism if it remains viable in the current funding environment.

Year End Progress Summary:

Sequencing DNA from brain tissue to identify fungal sequences proved more difficult than anticipated. The original method selected for analysis of fungal burden in brain tissue was ultimately not available. The Translational Genomics (TGen) Integrated Microbiomics Center had been selected as the sequencing lab because of their previous success in detecting low levels of bacterial DNA from brain tissue samples, which is technically difficult. However, when this project began, TGen was having difficulty with their 18S rRNA sequencing methodology and not accepting samples for analysis. Since their expertise in handling low biomass samples has been cultivated and is not readily available at other sequencing labs, we chose to continue the work using other methods. We started with a broad-spectrum fungal detection analysis via the Femto Fungal qPCR kit to establish the overall positivity rate in our samples. While the kit had reagents for creating a standard curve, we did not have a low biomass positive control sample from brain tissue, which would have helped to assess the ability of the kit to detect low levels of fungal DNA. Using this kit, we were only able to identify a few potential (very low level) positives in the 48 samples tested.

As the low-level detection capabilities of the Femto Fungal kit weren't clear, we moved forward with testing for specific fungi and fungal molecules. To assess whether fungal DNA was present in subject brain tissue, we used a qPCR kit that specifically detects the presence of Candida species DNA. This fungal genus was chosen for analysis because it is common in the human body. Using this method, we found that ~10% of tissues from both the SFG and MTG were positive for Candida DNA, although differences between subject groups were not statistically significant. To explore the presence of fungal components other than DNA in SFG brain tissue, we used two ELISA analyses. The first analysis detected antigens specifically from Candida albicans, the most common fungal organism inside the body. Using that analysis, we found that around 50% of the subjects in each of our four subject groups were positive for Candida antigens in their SFG brain tissue. Again, there were no statistically significant differences between subject groups. We then used a second ELISA test to detect beta-D-glucan, a common cell wall component present in the majority of fungal organisms. Using this test, we found that varying levels of fungal beta-D-glucan were present in the SFG brain tissue of all 48 tested subjects, with a statistically significant difference between normal and high pathology controls, but not other subject groups. This provides reason to suspect that additional fungi aside from Candida albicans may also be present in the brain, and we will further pursue that work to provide data that is complete enough for publication.

As indicated in the original proposal, we intend to combine our previous bacterial data with the fungal information to provide a more complete assessment of the brain's overall microbiome. We plan to use the combined data in grant applications to further explore how the microbiome affects

brain function and what its relationship is to Alzheimer’s disease and other neurological disorders. Our goal is to submit an NIH R21 grant proposal to support continuation of this work.

ARIZONA ALZHEIMER'S CONSORTIUM
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Design, Synthesis and Testing of Novel Compounds for the Treatment of Alzheimer's Disease. Volkmar Weissig ScD, PhD, Mark J Olsen, PhD. College of Pharmacy, Midwestern University; Arizona Alzheimer's Consortium.

Specific Aims:

Specific Aim #1: Synthesis of novel MMF prodrugs.
- Sub-Aim 1.1: Synthesis of amino acid type MMF prodrug esters.
- Sub-Aim 1.2: Synthesis of carnitine type MMF prodrug esters.

Specific Aim #2: Evaluation of novel MMF prodrug's ability to trigger mitochondrial biogenesis.
- Sub-Aim 2.1: Measurement of mitochondrial biogenesis in neuronal cell type.

Specific Aim #3: Evaluation of plasma stability of novel MMF prodrugs.
- Sub-Aim 3.1: Measurement of MMF prodrug ester mouse plasma stability.
- Sub-Aim 3.2: Identification of MMF prodrug ester plasma cleavage products

Specific Aim #4: Measurement of plasma and brain concentrations and preliminary pharmacokinetics.
- Sub-Aim 4.1: Quantification of mouse brain and plasma concentrations of MMF.

Background and Significance:

Alzheimer's Disease (AD) is a devastating dementia with well-known mitochondrial dysfunction. This project is designed to advance a brain-concentrating, mitochondrial biogenesis stimulating drug development program for the treatment of AD that is chemically compatible with oral disintegrating tablet (ODT) dosage forms.

Nrf2 activators are a known mechanism for triggering mitochondrial biogenesis, are FDA approved and have been on the market for more than a decade for the treatment of Multiple Sclerosis (MS) and may have utility with other neurodegenerative diseases. Well known Nrf2 activating compounds include Dimethyl Fumarate (DMF), Monomethyl Fumarate (MMF) and recently approved omaveloxolone (OMA). MMF is a Nrf2 activator that triggers mitochondrial biogenesis as a key mechanism of action, although DMF/MMF mechanism of action also involves Nrf-2-independent biogenesis pathways. There is abundant evidence that MMF has potential for the treatment of AD in cell lines and animal studies, and the same exact drug/strategy should also be useful for Frontotemporal Lobe dementia, vascular dementia, Lewy Body Dementia, Parkinson's Disease and schizophrenia. Unfortunately, the ABCC1 transporter likely prevents a positive clinical result for the treatment of AD. Only 12% of the blood MMF concentration reaches the Central Nervous System (CNS) in humans due to a Log[Brain]:[Blood] of -1.163. Up to 60% of DMF is exhaled as CO_2 and never reaches the CNS due to peripheral metabolism in the TriCarboxylic Acid (TCA) cycle, and cysteine conjugates account for another significant fraction of the dose that also fail to penetrate the CNS.

The primary significance of this proposal is the creation of a novel brain concentrating prodrug that can realize a concentration of the drug 10-fold higher in the brain than in the blood and have desirable solubility and buccal absorption properties. Compounds that trigger the Nrf2 activation pathway are very well known but have detractors due to the limited results obtained to date that have been attributed to limitations of the Nrf2 mechanism. By addressing the poor brain biodistribution and excessive peripheral metabolism leading to CO_2, a dramatic increase in the efficacy of an appropriate Nrf2 activating compound can unlock the observed potential of Nrf2 activators realized in mouse model systems at higher doses. These Nrf2 activators such as MMF are also chemically **IDEAL** to serve as a pioneer cargo for a brain concentrating prodrug due to

very small molecular weight and good chemical solubility. The concept of utilizing an ODT formulation for geriatric patients with dysphagia is also not new, although this is particularly useful in the area of dementia/neurological disease. The use of buccal administration prevents drug exposure to acidic gastric fluid, eliminating a chemical weakness that prevented prodrug development. While simple Nrf2 activating cargo moieties are the initial objective of this proposal and should directly result in an FDA approvable therapeutic for neurodegenerative diseases and beyond, the promise is that this same strategy can be expanded to a range of other cargo molecules for treatment of CNS disease utilizing other mechanisms.

Preliminary Data, Experimental Design and Methods:

Specific compounds were designed using commercial medicinal chemistry software package StarDrop by Optibrium. The conceptual design and rational for the compounds is shown were already performed**.** Briefly, MJO-265 has already been synthesized. Purity was 99.3% by LCMS, and all yields were high as expected. MJO-330 is inspired by carnitine that could utilize the OCTN2 transporter to deliver MMF.

Methods

Specific Aim #1: Synthesis of novel MMF prodrugs.

Compounds will be synthesized using known, conventional methods.

Specific Aim #2: Evaluation of novel MMF prodrug's ability to trigger mitochondrial biogenesis.

Compounds will be evaluated for triggering mitochondrial biogenesis in SH-SY5Y neuroblastoma cell lines already on hand using the known protocol utilizing acridine orange 10 nonyl bromide[23].

Specific Aim #3: Evaluation of plasma stability of novel MMF prodrugs.

Plasma stability will be contracted to Eurofins Scientific in St. Charles, MO. LC/MS is capable of distinguishing between amino acid ester hydrolysis and MMF hydrolysis.

Specific Aim #4: Measurement of plasma and brain concentrations and preliminary pharmacokinetics.

Brain and plasma concentration of MMF will be measured for the top 4 compounds at Eurofins/Panlabs in Taipei, Taiwan using methods already established for MMF due to FDA approval. Because work will be performed in Taiwan using standard NIH protocols, MWU IACUC approval is not needed. 3 male ICR mice will be in each group, drug will be administered by tail vein IV injection. Animals will be sacrificed, brain and blood will be harvested, and MMF concentration will be quantified by LC/MS.

Proposed One-Year and Long-Term Outcomes:

Data from this MAAC grant will be used in the submission of a R61/R33 for the development of drugs at NINDS using funding opportunity number PAR-25-225. The significance of a drug for the treatment of the white working class in absolute numbers as opposed to percentages will be emphasized to account for changing priorities at NIH.

Collaboration with EU, and in particular Czech colleagues will be pursued. Previously, **PI Olsen** postulated that FTO inhibitors would be useful for the treatment of neurological disease states **(PCT/US2013/060934)**. Subsequently, **PI Olsen** received a MAAC grant in 2015 for the treatment of AD using FTO inhibitors. As a result of this work, a long-term collaboration with Dr. Petr Telenský was established. *In vitro* results of this effort have been published, and a manuscript concerning the recovery of memory in aged AD rats has been written and is ready for submission. This emphasizes the long-term aspect of drug design, and the length of time required to develop and demonstrate a new therapeutic approach. The strategy described in this proposal is not nearly so radical and can likely be implemented in a much shorter period of time. **PI Olsen** has a long track record of productive collaboration with Czech colleagues, which allows for compounds and investigations to be funded outside of an NIH funding mechanism. While this

does not allow for MWU to receive grant money, it allows for the work to proceed. **Co-PI Weissig** has been funded by the Arizona Alzheimer's Coalition concerning the utility of Vitamin B12 and has a long history of work concerning mitochondria and is the President of the World Mitochondrial Society.

Year End Progress Summary:

Most proposed compounds were synthesized, although carnitine-type compounds with quaternary charges decomposed upon purification. A commercial, professional synthetic chemistry company was contracted to synthesize the carnitine compounds, also without success.

These compounds can be synthesized, but may require a longer, more time-consuming and expensive synthetic route that were beyond the financial scope of this grant. This work is in progress using other funding mechanisms.

Compounds were evaluated for plasma stability, with "flavored" compounds surprisingly being highly resistant to plasma hydrolysis. This unusual and surprising result meant that the desired prodrug could not be properly released in the blood. Normally, drugs fail because of insufficient plasma stability. This is an unusual case where there was unexpected stability and can likely be addressed by utilizing a slightly different drug design that should guarantee plasma hydrolysis.

Targeted, released compounds were experimentally confirmed to trigger mitochondrial biogenesis.

A selected compound that utilizes the LAT1 brain penetration mechanism was tested at one-hour timepoints for oral (PO) and intraperitoneal (IP) and full intravenous (IV) pharmacokinetic analysis at 8 timepoints was performed. The initial results did not indicate any improved brain penetration relative to MMF. This experiment was then repeated, because the results were surprising. The second round of experiments also indicated low brain penetration.

The proposed solution is to utilize the carnitine-derived compounds mentioned above that require a more difficult synthesis. The desire was to get a strong preliminary result to enable submission for a larger NIH grant, but additional effort will be required to deal with each individual issues. None of these issues are "deal breakers", but each will require some modification to the compound design and synthesis, and compounds will need to be confirmed to be labile in plasma to release the desired brain penetrating prodrug.

There is nothing wrong with the pharmacokinetic analysis, it was simply an issue that drug did not penetrate the brain better than the original drug MMF.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

The periphery of Alzheimer's disease: cross-talks between degenerating brain and peripheral tissues. Minsub Shim, PhD, Elizabeth Hull, PhD, Delrae Eckman, PhD. Midwestern University; Arizona Alzheimer's Consortium.

Specific Aims:

Specific aim: To characterize the molecular and cell biology of peripheral tissues during the development and progression of AD using 5xFAD and APP/PS1 mice

Alzheimer's disease (AD), a neurodegenerative disease with no known cure, was conventionally regarded as a disease affecting the central nervous system (CNS). However, growing evidence indicates that it is a systemic disease in which crosstalk between the CNS and peripheral tissues contributes to its pathogenesis.

Given the brain's important role in regulating peripheral tissues, it is also conceivable that impaired brain function in AD could negatively affect peripheral tissue homeostasis. However, research on changes in peripheral tissues during the progression of AD is surprisingly scarce, possibly because conducting longitudinal studies to identify changes in peripheral cells in living individuals is difficult. However, the use of animal models might be instrumental, as comparisons of changes in neuronal versus peripheral cells could be made with respect to disease development and progression.

In the proposed study, we hypothesize that altered neural metabolism in AD negatively affects peripheral homeostasis. We further hypothesize that peripheral cells in AD, a systemic disorder, recapitulate major molecular mechanisms affected in the brain. Therefore, this study aims to characterize the molecular and cellular biology of peripheral tissues during the development and progression of AD using 5xFAD and APP/PS1 mice, two well-established AD mouse models. Given the limited research on changes in peripheral tissues during AD progression, we believe the preliminary data from this project can be translated into a proposal for an NIH R21 or R03 application for biomarker identification and/or drug discovery.

Background and Significance:

AD is often associated with other comorbidities, including diabetes, cardiovascular disease, depression, inflammatory bowel disease, and loss of vision or hearing. Although it has not been determined whether these conditions are the cause or the result of AD, these findings suggest the systemic nature of AD. Interestingly, several studies have shown that exposure to young blood circulation by heterochronic parabiosis (i.e., a surgical procedure that connects two animals' circulatory systems, resulting in a shared blood circulation between 2 mice) or administration of young blood plasma (plasma from 2- to 3-month-old mice) reverses cognitive deficits observed in aged mice by increasing synaptic plasticity and hippocampal gene expression networks related to learning and memory. These findings suggest that the development and/or progression of AD is not only affected by neuronal loss but also by systemic circulating factors.

While these findings support the notion that AD is a systemic disease, more important questions to be answered are whether these changes are the cause or the result of AD. To answer this, it is important to know "when" these changes occur: before or after the significant loss of neurons in the brain. Identifying longitudinal changes in peripheral cells during the progression of AD in living individuals may not be feasible. However, it can be studied using well-established mouse models of AD.

The 5xFAD model is a widely used AD mouse model, accounting for 10% of all AD studies employing mouse models. Extracellular Aβ plaques can be observed at around 2 months and increase rapidly with age. At 6 months of age, plaques can be seen throughout the hippocampus and cortex and then develop in multiple brain regions. In addition, progressive neuronal loss occurs in the areas with the most pronounced amyloidosis. Almost complete neuronal characterization, including transcriptome analysis, was recently reported.

The APP/PS1 mouse strain, another commonly used model for AD research, exhibits a slower progression of plaque pathology than the 5xFAD strain. Aβ deposits can be detected as early as 4 months of age, accompanied by increased microglial and astrocytic activation. By 9 months of age, an increasing abundance of amyloid plaques can be found in the hippocampus and cortex. Between 8 and 10 months of age, modest neuronal loss was observed adjacent to amyloid plaques. Memory deficits, such as impaired contextual fear conditioning behaviors, can be observed as early as 6 months of age. Transcriptome analysis of the brain was also reported.

Preliminary Data, Experimental Design and Methods:

Twelve male and twelve female 5xFAD mice (6 transgenic males + 6 transgenic females + 6 wild-type males + 6 wild-type females) will be sacrificed at 1, 2, and 6 months of age. Similarly, twelve male and twelve female APP/PS1 mice (6 transgenic males + 6 transgenic females + 6 wild-type males + 6 wild-type females) will be sacrificed at 2, 6, and 9 months of age based on the reported timing of Aβ accumulation and memory deficit.

Before sacrifice and subsequent tissue harvest, the mice will undergo behavioral tests to assess their learning and memory. The tests performed will include the Y-maze test, the Novel Object Recognition test, and/or the Open Field test. The data from these tests will be analyzed using Any-maze software in my laboratory.

Following the sacrifice of the mice, tissues, including brain, heart, skeletal muscle, fat, aorta, carotid artery, spleen, small intestine, colon, liver, pancreas, kidney, thymus, lung, and reproductive organs, will be harvested. The harvested tissues will be frozen or fixed for histological/immunohistochemical and molecular analysis. In addition, blood will be collected via cardiac puncture, and plasma and white blood cells will be preserved.

Proposed One-Year and Long-Term Outcomes:

This funding will enable the following cross-disciplinary collaborations: (i) At the time points outlined above, we will conduct a longitudinal assessment of cardiovascular function (utilizing echocardiography) and at necropsy, isolate aortic/cerebrovascular segments for wire and pressure myography, respectively, in 5xFAD and APP/PS1 mice (Dr. Delrae M. Eckman, Associate Professor & MBS Program Coordinator, Biomedical Sciences Program) and (ii) *Ex vivo* brain cultures from 5xFAD and APP/PS1 mice will be used to assess a relationship between lysosomal dysfunction, the inflammatory response, and progranulin production and processing using MagPix assays and immunohistochemistry (Dr. Elizabeth Hull, Professor and Program Director, Biomedical Sciences). This funding will also enable the establishment and maintenance of 5xFAD and APP/PS1 mouse colonies at the MWU. Currently, faculty members at MWU are involved in research projects on various aspects of AD research. Thus, these strains of mice could be a valuable resource for the AD research community at MWU. The participating students will gain a deeper understanding of Alzheimer's disease through their involvement in the studies outlined in the Specific Aim. They will also learn and master various molecular/cellular, behavioral, and histopathological analysis techniques. Additionally, the students will improve their written and

oral skills in scientific communication by participating in manuscript writing and presenting their findings at scientific meetings.

Year-End Progress Summary:

Although we had difficulty mating APP/PS1 mice, we were able to produce experimental mice for the project. We did not observe any pathology in 5x FAD, APP/PS1, or control mice. The mice also gained normal weight. Based on the Y-maze test, we observed that 6-month-old 5x FAD and 9-month-old APP/PS1 mice have memory/cognitive deficits. The results of novel object recognition are currently being analyzed. Additionally, glucose control was slightly impaired in the 6-month-old 5x FAD mice. Molecular and histopathological analysis of other tissues, including skeletal muscle, liver, and pancreas, is in progress. Additionally, echocardiography was performed in these mice, and the results are being analyzed.

Although the histopathological analysis is ongoing, the notable observations in the liver of 6-month-old 5xFAD mice include pronounced microvesicles and vascular changes around the triad. Additionally, we also found an increased number of (i) p-H2AX-positive cells in the pancreas and (ii) CD45-positive cells in the fat tissues of 5X FAD mice, suggesting altered metabolic homeostasis in 5X FAD mice. We will conduct Aβ immunostaining of the brains to assess correlations between these markers (e.g., p-H2AX and CD45-positive immune cells) and the severity of Aβ accumulation. As we are getting more data, we will write a manuscript from this project. We will also work on submitting a research proposal to the NIH/NIA. Additionally, the findings from this study will be presented at the 2027 MWU Research Day and the AAC annual conference.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Molecular mechanisms of altering gamma secretase activity by modulatory proteins. Mark J. Swanson, PhD and Nancy S. Bae, PhD. Midwestern University; Arizona Alzheimer's Consortium.

Specific Aims:

***Specific aim 1*. Determine if the GSMPs directly interact with target proteins and catalytic subunits of γ-secretase.** The *working hypothesis* for this aim is that the GSMPs will act as specificity factors by bringing target proteins to the γ-secretase complex.

***Specific aim 2*. Determine the effects of the GSMPs on the activity of γ-secretase in a yeast genetic system with target proteins with and without their cytoplasmic domains.** The *working hypothesis* for this aim is that the GSMPs will affect γ-secretase activity in our yeast system only when the cytoplasmic domains of the target proteins are present.

***Specific aim 3*. Determine the effects of mutations in γ-secretase on the ability of GSMPs to alter activity and colocalize with the complex.** The *working hypothesis* for this aim is that the GSMPs will interact with γ-secretase by binding the amino termini of the catalytic subunits.

Background and Significance:

Alzheimer's disease (AD) is a slowly progressing neurological disorder that results in irreversible cognitive impairment and memory loss, affecting millions of elderly people worldwide. One pathological hallmark of AD is the accumulation of small peptides in the brain that form insoluble plaques and interfere with normal cellular functions. The peptides originate from the amyloid precursor protein (APP), a protein expressed on the cell surface with an external segment, a transmembrane domain that holds the protein in the membrane, and an internal domain. β-secretase cleaves APP, producing a fragment of the protein made up of the carboxyl(C)-terminal 99 amino acids (C99), that remains embedded in the plasma membrane. The γ-secretase protein complex cleaves C99 into two fragments, amyloid β peptides that are typically 40 or 42 amino acids in length (Aβ40 and Aβ42, respectively) and a cytoplasmic fragment called the amyloid precursor protein intracellular domain (AICD), which is released from the plasma membrane and enters the nucleus where it affects gene expression. The Aβ40 peptides are soluble and are the predominant form. Aβ42 peptides are less frequently produced, but they are insoluble. Normally, Aβ42 peptides do not accumulate into plaques. However, some circumstances can lead to an increase in Aβ42 production or a change in the Aβ40:Aβ42 ratio that can lead to Aβ42 deposits forming, resulting in AD pathology. γ-secretase is a multi-subunit protein complex that contains a catalytic subunit, either presenilin 1 or 2 proteins (PS1 or PS2).

Based on its relevance to Aβ peptide production, γ-secretase has been a target for therapeutic intervention. However, γ-secretase has 148 additional target proteins, so directly inhibiting γ-secretase to prevent Aβ formation and accumulation may inhibit many other cellular functions. Recently, regulation of γ-secretase is being explored through naturally occurring proteins that modulate its activity. Several γ-secretase modulatory proteins (GSMPs) have been identified, each interacting with γ-secretase. The γ-secretase activating protein (GSAP) was shown to increase APP cleavage but not Notch1 cleavage. The hypoxia inducible transcription factor 1α (HIF-1α) increased cleavage of Notch1 but was not tested with APP. IFITM3 (Interferon-induced transmembrane protein 3) is a protein known to have an effect during an innate immune response, and it increased the activity of γ-secretase on APP while lowering that on Notch1. Stress-associated endoplasmic reticulum protein 1 (SERP1) also increased cleavage of APP, but the cleavage of Notch1 was unchanged.

Preliminary Data, Experimental Design and Methods:

Specific Aim 1: Using affinity-tagged proteins expressed in *E. coli*, we will test direct interactions between GSMPs and the cytoplasmic domains of γ-secretase substrates, including APP, Notch1, N-cadherin, and ErbB4. We will also examine interactions between GSMPs and the amino-terminal regions of presenilin-1 (PS1) and presenilin-2 (PS2), which we hypothesize serve as GSMP docking sites. Finally, we will determine whether GSMPs, substrate cytoplasmic domains, and presenilin amino termini can form ternary complexes, supporting a model in which GSMPs recruit specific substrates to γ-secretase.

Specific Aim 2: γ-secretase complexes containing either PS1 or PS2 will be expressed in *Saccharomyces cerevisiae* together with substrate-GAL4 reporter fusions, allowing cleavage activity to be measured through activation of GAL4-responsive genes. We will compare cleavage of full-length substrate fragments from APP, Notch1, N-cadherin, and ErbB4 with cleavage of constructs containing only their transmembrane domains. If GSMPs enhance γ-secretase activity through interactions with substrate cytoplasmic domains, their modulatory effects should be lost when these domains are removed. These experiments will also establish whether GSMPs can regulate PS2-containing γ-secretase complexes.

Specific Aim 3: Using presenilin amino-terminal deletion mutants and selected dementia-associated presenilin variants, we will assess their effects on γ-secretase activity and GSMP-dependent modulation in the yeast system. In mammalian cells, we will test whether GSMPs co-localize with PS1- and PS2-containing γ-secretase complexes and whether disruption of presenilin amino termini alters this localization. We will also evaluate the effects of these mutations on substrate processing and determine whether multiple GSMPs can associate with the same γ-secretase complex, providing insight into the mechanisms governing GSMP recruitment and regulation.

Proposed One-Year and Long-Term Outcomes:

This work will provide insight into the mechanisms for the production of amyloid peptides leading to plaque formation, a hallmark of AD. GSMPs that specifically increase the activity of γ-secretase cleavage of C99 to produce amyloid beta peptides could be useful therapeutic targets by determining how to disrupt their interaction with γ-secretase in a manner that does not affect other target proteins. The GSMPs may be novel AD-susceptibility loci if their mutations can increase amyloid beta production in an uncontrolled manner. This could be important for determining the risk for the development of AD. The methodologies described will also form the basis for future studies to identify and categorize additional presenilin mutations and novel GSMPs. The use of multiple γ-secretase target proteins will allow us to determine if the GSMPs are highly specific or if they specify a subclass of targets, which will be important in predicting whether therapeutic intervention focused on those GSMPs will likely lead to off-target side effects. The proposed research will be used to train two technicians and two students. Data obtained from previously funded MAAC proposals has provided preliminary data for state and federal grant applications and for publication (Swanson *et al.* 2023). The data obtained from the studies proposed in this application will be used as preliminary data for the submission of federal grants to the National Institute of Aging, the National Institute for General Medical Sciences, or the National Science Foundation. Any data obtained will also be used for publications.

and paste from approved project proposal.

Year End Progress Summary:

Significant progress has been made toward **Aim 1**, which focuses on defining direct interactions among GSMPs, γ-secretase substrates, and presenilin catalytic subunits. Using affinity-tagged proteins expressed in *E. coli*, we confirmed that RAP1 interacts directly with both the amino terminus of PS1 and the APP intracellular domain (AICD). In contrast, no direct interaction was

detected between the PS1 amino terminus and the AICD. These findings support our working model that RAP1 may function as a molecular bridge that links the C99 substrate to the γ-secretase complex, thereby facilitating substrate presentation and cleavage. To extend these studies, we have cloned the cytoplasmic domains of Notch1, ErbB4, and N-cadherin into expression vectors for production of affinity-tagged proteins and are currently testing their interactions with both the AICD and the PS1 amino terminus. In parallel, the remaining GSMPs have been successfully cloned into tagging vectors, expressed, and shown to be soluble, enabling ongoing interaction analyses. We have also generated a large panel of Alzheimer's disease-associated mutations within the PS1 amino terminus and are testing their ability to interact with RAP1. To date, none of the mutations examined has disrupted the RAP1–PS1 interaction.

Progress has also been made toward **Aim 2**, which examines GSMP-mediated regulation of γ-secretase activity using a reconstituted yeast system. While establishing and optimizing the model, we observed that simultaneous introduction of multiple plasmids often resulted in variable activity among transformants, with some showing a complete loss of reporter activity. This issue was resolved by introducing plasmids sequentially, although this increased the time required to generate strains from approximately one week to three weeks. To improve throughput, we have begun redesigning the system by integrating γ-secretase subunits into the yeast chromosome, thereby reducing the number of required transformations. Importantly, the current system has already demonstrated biological validity. Expression of GSAP produced an approximately two-fold increase in GAL4 reporter activity, consistent with its known stimulatory effects on γ-secretase activity in human cells. RAP1 produced an even more pronounced effect, increasing reporter activity by approximately ten-fold. We are now constructing additional substrate reporters containing either the transmembrane domain alone or the transmembrane domain together with the cytoplasmic domain from APP, Notch1, N-cadherin, and ErbB4. These constructs are at various stages of cloning and introduction into the redesigned yeast system. In addition, PS1 and PS2 constructs lacking their amino-terminal domains have been generated for functional analysis.

For **Aim 3**, which investigates the role of presenilin amino termini in GSMP-dependent regulation and localization, we have demonstrated that RAP1 co-localizes with γ-secretase complexes containing PS1 in human cells. However, progress on equivalent PS2 studies has been hindered by the lack of suitable antibodies capable of reliably detecting PS2 in immunofluorescence assays. To address the mechanistic role of presenilin amino termini, expression constructs encoding amino-terminal deletion mutants of both PS1 and PS2 have been generated and are ready for testing. We are also constructing epitope-tagged versions of the GSMPs to simplify future co-localization experiments and reduce the number of antibodies required, thereby lowering experimental costs and improving assay flexibility. Although development of these reagents is time-intensive, they will provide critical tools for determining how GSMPs associate with γ-secretase complexes and how presenilin amino-terminal domains contribute to these interactions.

Data from this work was presented as a poster at the 2026 American Society of Biochemistry and Molecular Biology (ASBMB) annual meeting at the National Harbor DC Metro Area: March 7th - 10th.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Physiological and anatomical hallmarks associated with intermittent hypoxia and aging – insights into respiratory dysfunctions associated with Alzheimer's disease. Ann Revill, PhD, Glauber da Silva, PhD, Daniel Zoccal, PhD, Consultant: Pamela Potter, PhD. Midwestern University; Federal University of Minas Gerais; São Paulo State University; Arizona Alzheimer's Consortium.

Specific Aims:

1. Elucidate breathing modifications associated with aging and chronic intermittent hypoxia (CIH) exposure. Using mature (3-mo-old) and old (18-mo-old) adult mice (male and female) exposed to CIH for 10 days or normoxia (control), we will test the hypothesis that old mice will present greater respiratory variability than young mice and that these aging-related breathing changes are exacerbated by CIH exposure. We will test these hypotheses by employing whole body plethysmography methods to examine changes in breathing pattern and variability.

2. Determine postsynaptic excitatory muscarinic receptor expression and changes in cholinergic inputs to respiratory-related brain regions in response to aging and CIH exposure. We speculate that acetylcholine signaling may be a positive compensatory mechanism in response to CIH-exposure. Using brain tissue from the same cohorts of mice from Aim 1, we will test the hypothesis that CIH-treated mice will exhibit a net increase in postsynaptic excitatory muscarinic receptor expression and a net increase in cholinergic inputs to respiratory-related brain regions and that this effect will be blunted with advanced age. We will employ immunofluorescence to determine the relative expression of muscarinic excitatory (M1, M3, M5) and inhibitory receptors (M2) and of cholinergic inputs in mature and old mice exposed to CIH or normoxia in brain regions involved in the generation of inspiratory activity to airway muscles: preBötzinger Complex (preBötC), site of respiratory rhythm generation and hypoglossal motoneurons (XII MNs), innervating the tongue.

Background and Significance:

The proportion of people over 60 years will nearly double by 2050 and represent 22% of the population worldwide. Studies exploring the aging-related molecular and cellular mechanisms leading to organ and system dysfunctions are timely. Both Alzheimer's disease (AD) and obstructive sleep apnea (OSA) limit significantly people's quality of life and have increased incidence with age. Furthermore, the incidence of AD is increased in people with OSA. Thus, we must understand how normal aging and OSA affect the control of upper airway tone as an initial step before investigating respiratory dysfunction links between OSA and AD.

The tongue, innervated by the XII nerve, is a major upper airway dilator muscle and research into tongue motor control is likely to provide insights into OSA pathogenesis. The inspiratory activity of XII MNs is primarily driven by the respiratory rhythm generated by preBötC. XII MN activity is also highly influenced by neuromodulators that modify tongue activity, especially during sleep-wake states. For example, tongue atonia is observed during sleep, favoring the occurrence of airway obstructions. Recent indirect evidence suggests that activation of muscarinic acetylcholine receptors may mediate the diminished tongue muscle activity observed during REM sleep. XII MNs express these muscarinic acetylcholine receptors, which can be subdivided into two broad categories. M2 receptor has the overall effect of decreasing neuronal excitability. Conversely, M1, M3, and M5 receptors lead to an increase in neuronal excitability. Thus, the

ensemble effect of muscarine receptor activation on XII MN excitability will depend on the balance of excitatory and inhibitory muscarinic receptor expression levels. Muscarinic receptor antagonists have been tested as part of pharmacotherapy to reduce the severity of sleep apnea through actions in the XII MNs, highlighting the critical role of cholinergic transmission in the control of upper airway motor activity. However, little is known about changes in muscarinic acetylcholine receptor expression levels due to neuronal plasticity in XII MNs, like that induced by CIH and aging – factors directly associated with AD.

Therefore, understanding the isolated and combined effects of aging and CIH on the neuromodulatory control of upper airway muscles is the first step before exploring their association in the context of respiratory dysfunction associated with AD. In this study, we will test the hypotheses that CIH will promote increased excitatory muscarinic receptor expression within and increased cholinergic inputs to XII and preBötC in young adult animals in parallel with breathing alterations, and this effect will be blunted in older subjects because of decreased neuronal plasticity with aging, further affecting breathing stability.

Preliminary Data, Experimental Design and Methods:

The overarching scientific goal of this proposal is to characterize the changes in breathing and determine the associated changes in muscarinic receptor expression patterns and cholinergic inputs as a function of aging and CIH exposure. This series of experiments will provide valuable preliminary data for future planned experiments dissecting the mechanisms underlying the functional changes that occur in the respiratory control network associated with aging and in response to CIH exposure.

Male and female mice will be exposed to CIH to mimic one of the most important aspects of OSA in terms of disease progression. Respiratory patterns will be monitored using whole body plethysmography and respiratory parameters will be recorded during periods of quiet breathing. After protocol termination, mice will be euthanized by transcardiac perfusion and brains fixed with paraformaldehyde for immunofluorescence experiments to test for changes in expression pattern or levels of muscarinic acetylcholine receptors in XII MNs, preBötC and hippocampus.

Proposed One-Year and Long-Term Outcomes:

Task	Year 1	Year 2	Post Completion
CIH protocol and WBP	x	x	
Immunofluorescence experiments	x	x	
Data analysis	x	x	
Manuscript preparation and submission		x	x
Develop grant proposal			x

Data generated from the Arizona Alzheimer's Consortium grant will be crucial for development of an NIH R15 or R01 application to explore the functional effects of CIH exposure on muscarinic modulation of airway tone. This grant will propose experiments that combine *in vivo* recordings as well as additional neuroanatomy tracing experiments to evaluate the functional effects of CIH-exposure in mature and older rodent models.

Year End Progress Summary:

In this second reporting year, the AAC Developmental grant has permitted the following:

1) Data from these experiments has been presented at two American Physiological Society Summit conferences: 1) from April 24-27, 2026 in Baltimore, MD (Jeff Haney presented a

poster titled “Effects of aging and CIH exposure on respiratory function, postsynaptic excitatory muscarinic receptor expression, and cholinergic inputs”). 2) from April 23-26 in Minneapolis, MN (Payton Carlblom and Aliya Kammerer presented a poster titled, “Effects of aging and intermittent hypoxia on respiratory control in mice**”).** Preliminary findings indicate that older mice have lower respiratory variability compared to younger mice, whether or not they are exposed to CIH, and these results are expanded below.

2) Eight students have been trained on this project. Jeff Haney (2nd year medical student) completed a KAS Summer Research Fellowship in 2024, Julius Vellutato (3rd year medical student) completed a research elective in 2025, and Aliya Kammerer (1st year medical student) and Payton Carlblom (1st year medical student) completed summer research fellowships in 2025. In 2026, 4 students were recruited for this project: Alexa Thomas (KAS Summer Research Fellow), Faizan Mistry, Tony Orlando Lazo, Grace Thompson were recruited to complete data collection for this project. Thus, as well as advancing scientific knowledge, this project is providing excellent scientific training opportunities for future clinicians.
3) Based on reviewer feedback, we expanded our immunofluorescence analysis. As well as respiratory-related brainstem regions, we now also collect hippocampal brain sections and have confirmed that we can visualize M1 receptor expression there. This will increase the impact and relevance of our analyses as it will allow us to interrogate whether there are changes in muscarinic acetylcholine receptors in brain regions strongly affected by AD. We have outsourced the immunofluorescence experiment data collection to facilitate completion of the project.
4) We continue to strengthen the relationship with Co-PIs, Daniel Zoccal and Glauber da Silva, through our ongoing journal club and through a review article recently published in the Journal of Neurophysiology (Osbourne A, Melliza A, Dudley SK, da Silva GSF, Zoccal DB, Revill AL. 2025. Cholinergic modulation of upper airway control: maturational changes and mechanisms at cellular and synaptic levels. ***Journal of Neurophysiology***. 133(1):46-59. doi: 10.1152/jn.00165.2024). In addition, Dr. Zoccal has recruited a Masters student to his laboratory, who will complete complimentary experiments to those proposed herein, performing electroencephalogram (EEG) recordings to evaluate how CIH affects respiratory patterns and sleep architecture with aging.

Preliminary data. Our data in 18-month-old mice indicate that there is a shift in respiratory pattern towards an increase in tidal volume and an increase in inspiratory time in mice exposed to CIH compared to their naïve controls. The effects on respiratory pattern in 3-month old mice appear to be much smaller. Any change in total ventilation might be secondary to modifications in metabolic rate in response to CIH exposure. We have evaluated baseline oxygen consumption and carbon dioxide production in naïve and CIH-treated animals, which will allow us to correlate ventilation to metabolism. To our surprise, we saw a decrease in respiratory variability in both 3-month old and 18-month old mice exposed to CIH compared to their naïve controls. And, overall, respiratory variability is lower in 18-month old mice compared to 3-month old mice, regardless of CIH exposure. Future research will evaluate whether this change in respiratory variability affects the response to respiratory challenges such as chronic hypoxia or chronic hypercapnia.

Plan for post-award. We will complete all plethysmography data analysis, including metabolic analysis, as well as the immunofluorescence analysis and prepare a manuscript for submission. We plan to develop an NIH R15 or equivalent application to study further the effects of aging and CIH on the control of breathing. We will propose to evaluate how young and old mice exposed to CIH respond to respiratory challenges since as chronic hypoxia or chronic hypercapnia.

NORTHERN ARIZONA UNIVERSITY
PROJECT PROGRESS REPORTS

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report
NAU-PMI

Microbiome modulation of vagal afferent signaling. Emily K Cope, PhD, J. Gregory Caporaso, PhD, Carol Barnes, PhD, Katalin Gothard, MD, PhD, Mario Romero-Ortega. The Pathogen and Microbiome Institute, Northern Arizona University; University of Arizona (Tucson); Arizona Alzheimer's Consortium.

Specific Aims:

Specific Aim 1 (UA). Develop the technology to manipulate the gut and measure resulting vagal nerve outcomes.

Specific Aim 2 (NAU). To determine what microbiome metatranscriptomic and metabolomic features are associated with vagal nerve activity.

Specific Aim 3 (NAU). Conclude meta-analysis of AD microbiome assessing consistency of signals observed across different projects while using standardized analytic workflow.

Background and Significance:

Disruptions to the gut microbiome-brain axis have been linked to a range of diseases and disorders affecting brain, including anxiety and depression, Parkinson's disease, autism spectrum disorder, and Alzheimer's disease (AD). The emerging role of the gut microbiome in modulation of neurotransmitters has garnered recent attention, and there is appreciable evidence that select microbiota in the gut produce GABA, norepinephrine, dopamine, and serotonin/serotonin precursors. In addition to synthesizing neurotransmitters, gut microbes produce a variety of metabolites, such as short-chain fatty acids and bile acids, that can activate enteroendocrine cells, which in turn form synaptic connections with the vagus nerve. Understanding how gut-derived signals are transmitted to the brain is therefore essential for identifying the mechanistic links between the microbiome and neurological health.

Preliminary Data, Experimental Design and Methods:

With support of the AAC, we have recently published a study that demonstrated unique temporal gut microbiome signatures in 3xTg-AD mice and genetic controls (WT). Three statistical approaches used in this study (ANCOM, Random Forest machine learning, and volatility analysis) demonstrated increased relative abundance in Bacteroides in 3xTg-AD mice. Using shallow shotgun metagenomics, which allows for higher taxonomic resolution over amplicon sequencing, demonstrated the presence of several *Bacteroides* species, including *B. fragilis* in 3xTg-AD mice. Next, we supplemented mice with *B. fragilis* monthly for 52 weeks and observed consistent and early colonization of *B. fragilis* in 3xTg-AD mice and delayed colonization in WT controls. This suggested to us that there was a niche available early on in 3xTg-AD mice that allowed for *B. fragilis* colonization. In this study, we also observed an increase in *gfap* gene expression, indicating gliosis, in 3xTg-AD mice not supplemented with *B. fragilis*, as expected. However, when mice were supplemented with *B. fragilis, gfap* expression did not increase with age. We also observed a significant decrease in *slc1a3*, an astrocyte glutamate uptake receptor, in 52-week-old 3xTg-AD mice supplemented with *B. fragilis* compared to 3xTg-AD mice given a sterile vehicle control. Using untargeted metabolomics, we found that *B. fragilis* modulated several brain and gut metabolites in 3xTg-AD mice, returning them to levels observed in WT mice. This study is currently under review at mSystems and is currently available as a pre-print on BioRxiv (https://doi.org/10.64898/2026.05.29.728805). These findings, along with evidence from previous studies, suggest that *Bacteroides fragilis* may exert neuromodulatory effects; however, the underlying mechanisms remain poorly understood.

The overall goal of the first two Aims was to develop the technology to measure vagus nerve activity while altering the composition of the gut microbiome. Driven by our preliminary results, we focused on the bacterium *B. fragilis*. We prepared *B. fragilis* cultures in an anaerobic chamber. To assess whether live bacteria were required for modulation of vagus nerve activity, we prepared live cultures, heat-killed *B. fragilis*, and sterile bacterial culture media. At the University of Arizona, Drs. Barnes and Gothard performed surgeries and recordings of the rat vagus nerve using a "sutrode" electrode. *B. fragilis* live and heat-killed cultures were instilled into the gut via a surgically implanted duodenal catheter.

The goal of Specific Aim 3 was to complete a meta-analysis of the gut microbiome across human with AD and preclinical AD, and animal models of AD pathogenesis using a standardized bioinformatic approach to facilitate comparisons across groups. We performed this analysis using QIIME2 amplicon 2026.1 distribution.

Proposed One-Year and Long-Term Outcomes:

The data obtained from these experiments will be used to prepare an R01 grant to study not only vagal main trunk nerve activity after microbiome manipulation. Depending on the specific outcome, we will want to propose to record activity first from the nucleus of the solitary tract, which receives afferent sensory input from vagal ganglion cells. If there are clear behavioral differences that arise from *B. fragilis* treatment, we will also propose to record from the amygdala and hippocampus to determine whether the balance of excitatory and inhibitory activity is altered in these structures. We will also use the discoveries made from the metabolomics and transcriptomic studies to predict specific microbial metabolic pathways to manipulate that will impact vagal function. Future studies will also include assessment of aging and Alzheimer's disease rodent models.

Year End Progress Summary:

The overall goals of this project were 1) to determine if we could develop a system that would allow us to directly record activity of the vagus nerve while altering the composition of the microbiota of the gut, and 2) complete a meta-analysis of AD microbiome assessing consistency of signals observed across publicly available datasets using standardized analytic workflow.

Toward, the first goal, we performed several sets of experiments with Drs. Barnes and Gothard, performed at UA, using a novel electrode invented by our colleague, Dr. Romero-Ortega ("sutrode"), which he has used to record activity from other peripheral nervous system nerves. The initial set of experiments aimed to determine whether we could isolate the cervical vagus nerve and record vagal units with the sutrode. Dr. Gothard was the primary surgeon for all experiments. The initial surgeries involved learning how to dissect the region around the vagus nerve and wrap and tie the sutrode without damaging the nerve or breaking the electrode. In these early experiments, we found two main confounding factors. First, we had high background electrical noise in the system and second, we observed artifacts due to the needle poke into the gut for the injections. Students from the Barnes lab were able to improve upon these confounding factors by creating a chronic duodenal catheterization system prior to the vagus nerve surgery that minimized artifacts associated with injections. The second issue to overcome was the high levels of background noise in the system, which was resolved to a large degree by the Romero-Ortega lab purchasing a new recording setup with better grounding capabilities. With the new recording system, we were able to isolate single vagal action potentials and verify that we were recording from the same cells throughout the experimental treatment components.

After the confounding factors identified in the first set of experiments were addressed, we provided Drs. Barnes and Gothard with *B. fragilis* ($1x10^9$ CFU/mL) and heat-killed *B. fragilis* (from $1x10^9$ CFU). *B. fragilis* was purchased through the American Type Culture Collection (ATCC) and propagated in an anaerobic chamber in TSA with defibrinated sheep blood. To identify potential metabolites or proteins that may interact with the vagus nerve via the gut, supernatant fluid was

prepared for metabolomic analysis (ongoing) and *B. fragilis* cells were prepared for transcriptomics (ongoing). This set of experiments performed at UA used live and heat killed *B. fragilis* in succession, administered through the duodenal catheterization system. The results from this recording demonstrate the ability to identify and separate single units using the sutrode, and it was observed that *B. fragilis,* both heat-killed, and to a greater extent, live bacteria decreased vagal nerve firing. However, there was a great amount of variability and an apparent continual diminution of firing across the entire course of the experiment (~4h). Thus, we did not achieve the stability of recordings to be able to clearly interpret the effects of *B. fragilis* on the vagus nerve. Our overall goal was to make these recordings in live, awake animals; however, this system does not appear capable of supporting that goal. Several challenges became apparent: surgical isolation of the vagus nerve was more difficult than anticipated, and both the sutrode and acute exposures appeared limited to a maximum of 3 hours, suggesting the method would not readily translate to chronic recordings. Alternative approaches will be needed to achieve continuous vagus nerve recording in awake, behaving animals with controlled gut microbiome manipulation. We plan to continue pursuing solutions to these barriers.

Toward the second goal, we were able to complete a meta-analysis across 11 datasets including human cohorts of cognitively impaired AD, preclinical AD, and cognitively normal controls, 3xTg-AD, 5xFAD, and APP/PS1 mice. Datasets were selected on their availability of sequence data in NCBI SRA and documentation of appropriate metadata. Studies were excluded if sequence data were not deposited in a public database or if the associated metadata were insufficient to perform group comparisons. Each dataset was denoised independently to account for study-specific sequencing characteristics. All datasets were assigned taxonomy against four common reference databases (Greengenes, Greengenes 2, GTDB, and SILVA 138.1) to allow for comparison of taxonomic signatures across each database within and across datasets. Alpha diversity was computed as Shannon entropy, Faith's phylogenetic diversity, observed features, and Pielou's evenness; beta diversity was computed as unweighted UniFrac, weighted UniFrac, Bray-Curtis dissimilarity, and Jaccard distance. Differentially abundant taxa were identified using ANCOM-BC applied to genus- and species-level collapsed tables from each dataset. Disease state (Alzheimer's disease vs. control) was the sole fixed effect, with control as the reference level. Beta diversity analysis demonstrated a consistently significant difference between AD and control groups using Unweighted Unifrac distances (10/11 datasets FDR corrected $p<0.05$, PERMANOVA). This is consistent with what was published for each study. When weighting by abundance of features (weighted UniFrac), we observed fewer significant differences (5/11 datasets FDR corrected $p<0.05$, PERMANOVA), indicating that the AD-associated signatures may be driven by lower abundance taxa. Differential abundance testing demonstrated significantly enriched or depleted features in AD/AD models, but the specific taxa differed across study and sometimes across the database used to classify taxonomic features. This highlights the need for standardized taxonomic classification methods, since apparent discrepancies may reflect methodological or experimental differences rather than true biological inconsistency. A manuscript reflecting these results is in progress and we anticipate publishing in a mid- to high-impact journal such as mSystems.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report
NAU-SBS

Development of Tailored Technologies and Resources to Identify and Support Rural Caregiver-Receiver Dyads with Mild Cognitive Impairment Due to Alzheimer's Disease: The Northern Arizona Memory Study. Michael J. McCarthy, PhD, Eric S. Cerino, PhD, Megan McCoy, PhD. Northern Arizona University; Arizona Alzheimer's Consortium.

Specific Aims:
Specific Aim 1: Strengthen and expand cognitive screening capacity and brain health resources in senior centers across rural Northern Arizona.
Specific Aim 2: Strengthen and expand partnerships with Indigenous-serving organizations developed in Years 1 and 2 and pursue formal approvals from the tribal councils of Navajo Nation, Hopi Tribe, and Hualapai Tribe in Peach Springs to conduct data collection for the Northern Arizona Memory Study on tribal lands.
Specific Aim 3: Evaluate the impact of modifiable, multi-level (e.g., individual, dyadic, family, geographic information systems, environmental) risk and protective factors on daily cognitive health among a representative sample (cognitively unimpaired, SCD, MCI) of individuals in rural Northern Arizona.

Background and Significance:
More than 6 million individuals in the U.S. live with Alzheimer's Disease (AD) and this number is expected to increase dramatically in the coming years[1–3]. AD is distressing for the individual facing symptoms, as well as for family caregivers who often serve as the primary source of daily support. This situation is exacerbated for "care dyads" living in rural areas who are isolated[4], underdiagnosed[4], have few resources[5], experience geographic barriers to care[6], and lack basic access to AD-related information and services[7,8]. Local senior centers in Northern Arizona offer unique potential to compensate for this lack of formal services in rural areas[9] but need to be more intentionally integrated into community-based screening efforts to address this gap in screening and outreach services. Community-based participatory approaches in rural communities that directly engage stakeholders can foster relevant service delivery, strengthen care networks, and support sustainability[10]. Despite these pressing needs and the potential value of senior centers as vehicles for screening, referral and provision of support, there are currently few interventions specifically designed to identify and support socio-culturally diverse rural families coping with AD, including early detection of potential precursors to AD such as Mild Cognitive Impairment (MCI) and Subjective Cognitive Decline (SCD), nor are there validated strategies for community-based delivery of support[11,12]. Without early detection and intervention, care dyads, particularly those living in rural areas, are left to cope in isolation, leading to additional individual, interpersonal, and community-level consequences. The long-term goal of the Northern Arizona Memory Study (NAZMS) is to develop accessible, culturally informed, and scalable intervention technologies and resources to identify and support diverse rural families coping with SCD, MCI, and AD. Our community-based, digital health approach to supporting care dyads emphasizes learning preferences for technology content and delivery modes, as well as protective factors associated with cognitive health among individuals with MCI. Community-based participatory approaches in rural communities that directly engage stakeholders can foster relevant service delivery, strengthen care networks, and support sustainability[10].

Preliminary Data, Experimental Design and Methods:
Previous studies and work by our interdisciplinary team from social work (McCarthy, McCoy) and psychological sciences (Cerino) well-position our team for success with this study [8,13–29]. Years 1

and 2 provided the foundation for our Year 3 Aims. In Year 1, we conducted a survey of Northern Arizona senior centers to assess current capacity and needs for brain health programming. We cultivated partnerships by delivering Brain Health Workshops to centers in Flagstaff, Yarnell, and Prescott, along with multiple tabling events in Flagstaff and Prescott that featured resource education, cognitive screenings, referral guidance, and enrollment in NAZMS. We engaged in formal outreach in Window Rock (capital of the Navajo Nation) by delivering presentations and roundtable discussions alongside Navajo, Hopi, and Zuni caregivers at a Caregiver Summit. We conducted semi-structured qualitative interviews with individuals with MCI and their family caregiver to determine needs and technology preferences for brain health support, as well as feasibility-tested our mobile protocol to examine the influence of modifiable contextual factors on daily cognitive health. We documented and presented to multiple audiences key needs for brain health support in Northern Arizona and technology preferences for receiving support. In Year 2, we deepened our existing partnerships in Flagstaff, Yarnell, Bullhead City, and Prescott and expanded to other senior centers across Northern Arizona including Prescott Valley and Snowflake. We engaged additional tribal partners through planning the first Hopi Caregiver Summit. We received conditional approvals from the NAU Office of Native American and Indigenous Advancement's Tribal Consultation process and NAU's Institutional Review Board to seek formal tribal IRB approval to expand recruitment to tribal lands. We developed the concept for the peer-led Brain Health Ambassador program through a series of workshopping sessions with 5 older adult "Brain Health Ambassador" volunteers from the Montoya Center in Flagstaff. Together, we outlined the components of a program which included peer-led education and promotion of brain health awareness, mapping protective factors for cognitive health to senior center activities, as well as technology-based Brain Health Kiosks where participants can complete memory self-screening and access online memory resources. We made refinements to our mobile protocol, including improving our process for enrolling participants and collecting data remotely, and continued to enroll individuals with MCI in Aim 3 of the study.

Specific Aim 1 for Year 3 was achieved by continuing to provide memory screening and referral events in senior centers with whom we have partnerships from Years 1 and 2 and by expanding to other senior centers across Northern Arizona. Specific Aim 2 for Year 3 was achieved by building on the NAU Office of Native American Initiative's conditional approval to reach out to Tribal Nations received in Year 2, by providing free memory screening and referral events in consultation with community partners from each tribe, and by thoughtfully pursuing letters of support and presentations to tribal councils. For Specific Aim 3 for Year 3, our plan was to continue to recruit participants and collect data in Year 3 using infrastructure we developed in Years 1 and 2. However, time constraints and, especially, opportunities to make significant progress on Specific Aims 1 and 2 described above led us to pause Specific Aim 3 work until the next funding cycle. Those activities will include making ongoing refinements to our mobile protocol and continuing to enroll individuals with MCI/SCD in the study in rural and remote areas.

Proposed One-Year and Long-Term Outcomes:

We anticipate that achieving the Year 3 NAZMS Aims will yield a high return on investment for the Arizona Alzheimer's Consortium and the Arizona community, at large. One year outcomes for Aim 1 include: 1) Formal partnership (i.e., with vendor form and/or memos of understanding) with six senior centers in Northern Arizona which will provide a conduit for disseminating and receiving data-driven information from the communities they serve. 2) A peer-led Brain Health Ambassador program, with associated Brain Health Kiosk, that is demonstrated to be feasible and acceptable to socio-culturally diverse rural families coping with MCI/SCD. A cumulative total of 20 older adults screened for MCI/SCD and referred to appropriate resources, as needed. One year outcomes for Aim 2 include formalized support from key leaders within the Navajo Nation, Hopi Tribe, and Hualapai Tribe, as evidenced by delivery of memory screening and referrals events on the respective tribal lands (with 10 Indigenous older adults screened and referred, as appropriate),

securing at least one Letter of Support from each tribe, and presenting about NAZMS to each tribal council. One year outcomes for Aim 3 include enrollment of an additional 25-30 individuals providing 14 days of mobile protocol data. This will yield a total sample size (Year 1, Year 2, and Year 3) of approximately 50 rural and socio-culturally diverse individuals who are cognitively unimpaired, with SCD, or with MCI. We will leverage 14 days of data to maximize statistical power (i.e., 50 respondents*14 days = up to 700 observations) when evaluating contextual protective and risk factors for daily cognitive health. More broadly, increasing the capacity of senior centers to efficiently and accurately screen for MCI and SCD is a critical step in combatting the national problem of undercounted adults with MCI, SCD, and AD. Efforts to strengthen and expand our current network of senior center partners, with the longer-term goal of co-creating culturally relevant resources and intervention technologies, will benefit the current study and, potentially, other Consortium members such as Matt Huentelman, Jessica Langbaum, and Lori Nissen who engage with these communities now and plan to continue in the future.

Year End Progress Summary:

One year outcomes for Aims 1 and 2 were achieved in Year 3 of the study. We currently have five formalized partnerships with senior centers in our region (Yarnell, Prescott, Bullhead City, Snowflake, Flagstaff). In Year 3, we conducted six community based education and outreach activities (Montoya Brain Health Fair, Arizona Indian Council on Aging/Family Caregiver Support Program Conference, Brain Health Workshop at the Flagstaff Public Library, presentations at Indigenous Brain Health Summit, Moenkopi symposium in August 2025, Community Partner CBPR Event at NAU-CHER) and five tabling events and similar outreach activities in Coconino, Mohave, Yavapai counties, as well as in Window Rock, Navajo Nation, and Polacca, Hopi (AICOA/FCSP Conference; Banner's "Shine A Light on All Dementias" event; August 2025 T-Gen event in Cottonwood, AZ; June 2026 Polacca, Hopi CHR event; Indigenous Brain Health Summit tabling), as well as nine Brain Health Ambassador meetings including filming a video introducing the Ambassadors and the Brain Health Kiosk concept to future users.

The peer-led Brain Health Ambassador and Brain Health Kiosk program located in Flagstaff's Montoya Senior Center is well-underway and we are developing strategies for replicating the program to other more remote communities. We co-created and evaluated for feasibility and acceptability the peer-led *Brain Health Ambassador* and tablet-based *Brain Health Kiosk* program through a series of workshopping sessions with an established partner in Flagstaff (Montoya Center patrons), culminating in a Brain Health Fair in April 2026 where the *Brain Health Kiosk* was introduced by *Brain Health Ambassadors*. Over 36 culturally-diverse individuals (plus Coconino County lunch program participants) attended the Brain Health Fair which included a pre-lunch presentation, resource tables from community organizations (e.g., Arizona Alzheimer's Association Support Group, NACOG, Oakwood Creative Care, Intertribal Council of Arizona), *Brain Health Ambassadors,* table "brain games," and two tablet-based *Brain Health Kiosks* which participants used to complete memory self-screening and access culturally-tailored supports (e.g., brain games, memory cue checklists, healthy aging strategies), and resources from the Arizona Alzheimer's Consortium (e.g., MindCrowd), NIH-NIA, and the Alzheimer's Association.

In Year 3, we engaged additional tribal partners through faculty and student participation in Banner's 19th Annual Conference on Alzheimer's and Dementia in Native Americans, by collaborating with the International Association for Indigenous Aging (IA2) around culturally-tailored materials development and dissemination, by tabling/presenting at local and regional events (30th Biennial Arizona Indian Council on Aging Conference; Polacca Hopi Community Health Representative Wellness Event, and others), by providing dementia caregiver education sessions (e.g., Hopi Tribe's Office of Aging & Adult Services dementia caregiver training series in summer 2025), and by co-sponsoring, planning, and delivering the first "Hopi Dementia Education Symposium" in Moenkopi in August 2025 to over 100 Indigenous caregivers, where we provided the keynote research address, sponsored a table with resources on brain health and opportunities

for future research participation, and supported a respite room staffed with study team student volunteers engaging people with dementia while caregivers attended the conference. We are currently co-sponsoring/planning (e.g., conference agenda, speaker engagement, provision of CEUs for attendees, etc.) the Indigenous Heathy Brain Summit Conference with the Navajo-based So' Tsoh Foundation, scheduled for June 25-26 at the Twin Arrows Casino. We have also committed to planning and supporting the second annual "Hopi Dementia Education Symposium" in November 2026 and have begun planning committee meetings for this event in June 2026. We have secured one formal letter of support from Hopi tribal leadership, which will be instrumental in our application for tribal IRB approval and are well-positioned to secure an additional letter from Navajo tribal leadership.

Our research team continues to actively develop and reinforce partnerships, as well as screen participants. To date, we have screened 47 rural individuals with MCI (n=17) and/or SCD (n=39) and enrolled 36 participants in Aim 3 of the study. Participant recruitment, data collection, and data analysis are ongoing. We continue to take advantage of opportunities to cultivate partnerships with healthcare providers in our region. Achieving our proposed one year outcomes is allowing us to progress toward the broad goal of increasing the capacity of senior center and tribal organizations to screen and intervene effectively with diverse adults with MCI, SCD, and/or AD living in rural areas. Our primary challenge is that participant recruitment for Aim 3 continues to progress at a modest pace because of the community-based methods we are committed to employing in order to promote long-term engagement from our senior center and other partners. These methods hinge on developing trust with the leadership, staff, and clientele of community-based organizations. This is especially true for tribal partners. Data we collected in Year 1 demonstrate that the large majority of senior centers in our target region have little to no experience engaging with research teams. Trust-building takes time but we are confident that our approach, rooted in established CBPR methods, will result in deep commitment from our partner agencies in the immediate and distant future.

Conclusion: Support from the Arizona Alzheimer's Consortium has allowed our interdisciplinary team to coalesce around our shared aging, MCI, and AD research interests and intervention development goals. We have conducted numerous presentations about project activities at regional and national conferences, as well as published findings in high-impact peer-reviewed journals (e.g., *JMIR Research Protocols*, *BMC Digital Health, Progress in Community Health Partnerships*, *Journal of Cross-Cultural Gerontology*). We are also leveraging Consortium support to move general aging and dementia workforce education initiatives in Northern Arizona forward (e.g., 2025 and 2026 NAU Interprofessional Dementia Education Event) with partners from across the state (e.g., Arizona Geriatrics Workforce Development Program subcontract with the University of Arizona).

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Development of a non-invasive assay of brain insulin sensitivity in humans. Travis Gibbons, PhD. Northern Arizona University; Arizona Alzheimer's Consortium.

Specific Aims:

1. To determine if neuron-derived extracellular vesicle (NDEV) -based analysis can detect changes in brain insulin signaling induced by intranasal insulin administration, and;
2. To test whether NDEV-based analysis can detect impairments in brain insulin signaling across the spectrum of AD progression.

Background and Significance:

Impaired brain glucose metabolism is a hallmark of Alzheimer's disease (AD), and evidence indicates that brain metabolic dysfunction *precedes* the onset of symptoms by a decade or more. This is not unsurprising given that the resting brain has an incredibly high metabolic rate and receives >95% of its fuel from the blood, which necessitates highly coordinated regulation of brain fuel delivery and usage. Thus, improving brain energy metabolism is at the forefront of many neuroprotective strategies. Unfortunately, assessing brain-specific metabolic health is a challenge. Whole-body insulin sensitivity tests are the gold-standard for evaluating systemic metabolic health. These tests provide a metric of metabolic function by quantifying glucose uptake in response to an insulin dose, and are used for diagnosing metabolic diseases, and as a metric to assess efficacy of interventions. Given that *brain-specific metabolic dysfunction* is a hallmark of AD, developing a test of brain insulin sensitivity would bridge a research gap in evaluating brain human brain health.

Preliminary Data, Experimental Design and Methods:

Study 1: NDEV's will be isolated from frozen plasma collected from the internal jugular bulb before and after a 50 IU dose of intranasal insulin. NDEV's will be evaluated for concentration of phosphorylated insulin receptor substrates. A total of 52 samples will be analyzed, representing 13 healthy human subjects tested twice in November 2023.

Study 2: Plasma will be acquired via the Barrow BioBank CORE facility, or, if necessary, via blood sampling conducted at in Flagstaff, AZ. Twenty samples will be analyzed from three cohorts: 1) healthy controls, 2) age-matched and diagnosed with MCI, and 3) age-matched and clinical diagnosis of AD. MCI will be classified according to the Petersen criteria and Clinical Dementia Rating global score of 0.5. Those with probable AD and mild to moderate dementia will be diagnosed by the Dubois criteria and have a CDR global score of 1.0. Cerebrospinal fluid concentration of amyloid-beta1-42 will be used if available.

Proposed One-Year and Long-Term Outcomes:

One year: Execution of NDEV isolation technique in human plasma.
Quantification of biomarkers of brain insulin signaling from isolated NDEV's.

Long-Term: Implementation of NDEV isolation technique in aging humans ranging the spectrum of pathology.
Exploration of biomarker analysis from isolated NDEV in aging humans ranging the spectrum of pathology.

Year End Progress Summary:

Within the last 10 months (07/01/2025 – 05/01/2026) we have made progress in developing the NDEV isolation technique from human plasma and serum. We had intended to measure P-serine 312-IRS-1 from isolated NDEV's, however, the assay was discontinued. We explored alternative downstream analytes and in collaboration with Neurodex Inc., decided to invest in an 11-plex Luminex kit that provides a more complete pathway analysis of brain insulin signaling (Figure 1). Neurodex Inc. first tested this multiplex assay on NDEV's pre- and post- a GLP1 agonist intervention to verify it will be effective in quantifying changes in NDEV's.

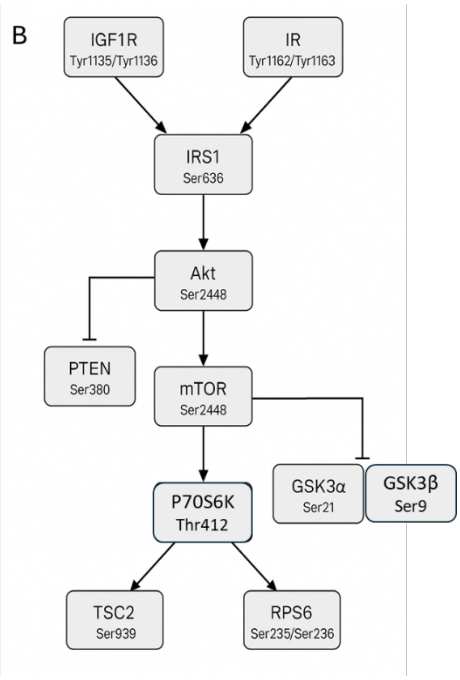


Figure 1. Downstream analytes being measured via the 11-plex Luminex assay from NDEV's. These analytes are to be quantified in blood entering (radial artery) and exiting (internal jugular bulb) the human brain pre- and 1-hr post- 52 IU of intranasal insulin.

Throughout this year we faced two major obstacles: 1) the assay we intended to use was discontinued and so we spent 2-3 months testing alternative options, and 2) the multiplex assay we chose to use in the end was more expensive than the original single analyte assay. As a compromise, we collaborated with a team at Neurodex Inc., including Dr Erez Eitan, who provided us a 40% discount pending we analyzed paired arterial and jugular venous samples. This academic collaboration with Dr Eitan provides mutual benefit as it is shared interest to better understand how sampling proximity to the brain, e.g., arterial, jugular venous or cerebrospinal fluid, influences biomarker concentrations isolated from NDEV's. Preliminary results revealed that sampling site is inconsequential and peripheral venous blood samples are satisfactory for NDEV biomarker analysis. This discovery will allow us to proceed with much less invasive techniques to interrogate brain insulin signaling in more vulnerable populations.

Preliminary results from the multiplex assay revealed that 52 IU of insulin administered intranasally – which has been shown to increase insulin concentration in the cerebrospinal fluid – did not influence the concentration of activated insulin receptors in isolated NDEVs. However, prolonged endurance exercise significantly increased activated insulin receptors in isolated

NDEV's (Figure 2). These data corroborate with our observation that exercise increases brain-specific insulin sensitivity in healthy young adults [1]. Thus, this novel assay provides us with a mechanism that explains why the brain is more responsive to insulin in the post-exercise state.

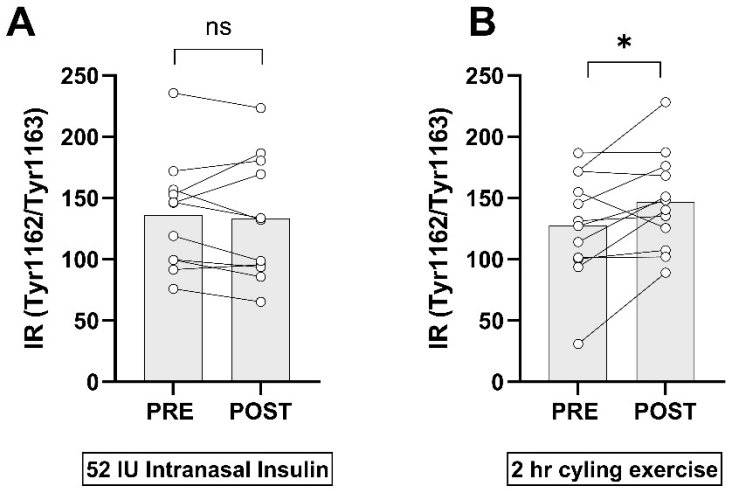


Figure 2. Activated insulin receptor (IR Tyr1162/Tyr1163) responses to intranasal insulin administration (A) and 2-hr of cycling exercise. * significant difference ($P<0.05$) between pre- and post- measures.

Future work:

We are continuing our collaboration with Dr Eitan and Neurodex Inc. with intentions of using this assay to characterize brain insulin signaling in healthy aging and in Alzheimer's Disease. We will be applying for continued funding from the AAC to determine whether these assays will be able to identify cerebral metabolic decline in the early stages of pathology.

2026 publications directly related to AAC Pilot Project Funding:

1. Carr JMJR, Koep JL, Duffy JS, Brewster LM, Bird JD, Monteleone JA, Monaghan TDR, Islam H, Steele AR, Howe CA, Thomas KN, MacLeod DB, Ainslie PN, **Gibbons TD** (2026) Exercise Increases the Sensitivity of Cerebral Glucose Metabolism to Intranasal Insulin in Young, Healthy Adults. *Journal of Neurochemistry*, 170(6):e70488. https://doi.org/10.1111/jnc.70488

TRANSLATIONAL GENOMICS RESEARCH INSTITUTE
PROJECT PROGRESS REPORTS

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Understanding genomic complexity in Alzheimer's disease and Lewy body dementia. John D. Fryer, PhD. Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:
Defining the landscape of genetic and genomic changes that occur in Alzheimer's disease (AD) and related dementias (ADRD) is an ever-evolving endeavor. Understanding the myriad changes that drive disease progression, as well as the alterations that occur due to disease processes, is critical in deciphering the pathogenesis and identifying potential therapeutic targets and pathways. Among the most common ADRD conditions, is Lewy body dementia (LBD) that shares many disease features and hallmarks in common with AD, including amyloid, tau, and synuclein pathologies. Our lab has generated the first large scale transcriptomic dataset of LBD and directly compared this against AD cases. As one might expect, there are many shared changes, but several unique alterations not only to clinicopathologic diagnosis, but also strong sex-specific changes. Our goal in this current project is to better understand these alterations using long-read sequencing methodologies, as this is particularly well-suited to understanding RNA isoform level changes in the context of the entire gene body.
Specific Aim(s)Aim 1. To understand the putative RNA isoform level changes in AD vs LBD brain tissue. Using existing datasets, we will determine the isoform changes that vary by disease status, pathological burden, and sex.
Aim 2. Determine isoform changes using discovery-based long-read RNA sequencing of representative AD and LBD cases. Utilizing a subset of cases from Aim 1, we will perform long-read RNAseq (PacBio Kinnex) to discover novel splicing changes in the context of the full-length RNA isoform.

Background and Significance:
We aim to clearly define the isoform-level changes that occur in both AD and LBD, using pathologically defined cases. To this end, we will re-analyze existing data that we recently generated and published in *Brain.* These samples comprise a large set of LBD cases (N=436), AD cases (N=53), and control cases (N=81) that we have already performed RNAseq using short read (Illumina) technology.

Preliminary Data, Experimental Design and Methods:
We have generated and analyzed bulk RNAseq data (short-read) from a large cohort of LBD cases and comparator AD group. These resulted in both shared and distinct overlapping gene alterations between these 2 diseases.

Proposed One-Year and Long-Term Outcomes:
Our one-year outcome is to complete Aim 1 using existing data, and to perform the long-read RNAseq. Our hope is to submit these for publication by the end of year 1, and to submit a larger proposal to the NIH to take a much deeper dive into isoform alterations across a larger case series. These will leverage Dr. Tom Beach's brain bank at ASU/Banner Sun Health.

Year End Progress Summary:
We have made substantial progress in our analysis of the existing short-read data. We have taken our large series of 570 cases across LBD, AD, and controls, and run them through splice-aware and ISOseq pipelines. As others have found, we find some differences between pipelines used (e.g. salmon, SplAdder, and MAJIQ), but have arrived at a consensus set of changes that look

robust and reliable. We have the additional advantage that our LBD cases are also comprised of pathological subtypes of LBD with synuclein only (LBD-S), with amyloid and synuclein (LBD-AS), or with amyloid and synuclein and tau (LBD-ATS). There are a lot of changes and data to unpack from this analysis, and we are debating whether this should constitute its own manuscript, or whether we should wait until we have analyzed the PacBio long-read data. Our inclination to wait until we have analyzed the long-read data and then integrate the findings into a large manuscript.

On that note, we have also made substantial progress on our long-read data. Because we were worried about effect sizes, we decided to supplement the proposed experiments with separate funds from Dr. Fryer and run a total of 288 samples across the groups, including expansion of this series to include the LBD subtypes. This type of data has not been generated before, and we are excited to contribute this to the field. We have now completed this data acquisition portion of this project, including the mRNA long-read library prep (Kinnex kit) as well as run across 48 PacBio SMRT cells. This represents an additional $120K investment from our lab to supplement the original goals. This sequencing is completed, and the initial QC metrics look outstanding (e.g. consensus quality scores and mapping rate). We have now begun the process of analyzing the isoform level differences between groups, and between sexes. Of note, we expect there to be numerous sex-based differences as we found for our bulk RNAseq dataset that we published last year on these same samples. We hope to complete these analyses and push to submit this ISOseq data for publication by the end of 2026.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Factors associated with longitudinal cognitive change in urban and rural Arizona. Matt Huentelman, PhD, Lee Ryan, PhD, Oana Dumitrascu, MD. Translational Genomics Research Institute; University of Arizona (Tucson); Mayo Clinic, Scottsdale, AZ; Arizona Alzheimer's Consortium.

Specific Aims:
Specific Aim 1: Demonstrate an ability to incorporate longitudinal visits in the mobile laboratory workflow.
Specific Aim 2: Measure DNA and protein biomarkers from 200 longitudinal mobile laboratory participants.

Background and Significance:
Rural zip code residents are significantly underserved and understudied in cognitive aging research despite elevated dementia risk. The MindCrowd mobile laboratory (MC-mLab) was created to bring multimodal research directly to communities across Arizona, including communities that have historically had limited access to cognitive aging research. During the 18 months before this grant period, the team recruited more than 1,200 participants. This grant supports expansion of biomarker analysis in the longitudinal MC-mLab cohort to identify factors associated with cognitive, MRI, and other phenotypic change over time.

Preliminary Data, Experimental Design and Methods:
The project evaluates blood and phenotype measures from 200 longitudinal mobile laboratory participants. Plasma biomarkers are measured using the Alamar NULISA CNS panel, a 120-plex assay focused on brain-related proteins. DNA methylation changes are assessed using Illumina BeadChip technology. Genome-wide SNP genotyping provides genetic context for biomarker interpretation. Statistical analyses evaluate cross-sectional values and longitudinal delta values to identify factors associated with cognitive, MRI, retinal, body composition, olfaction, blood pressure, and other phenotypic changes across time.

Proposed One-Year and Long-Term Outcomes:
One-Year Outcomes: We expect to successfully incorporate longitudinal profiling into the mobile lab protocol and assess ~200 participants. We will also complete plasma and DNA methylation biomarker assessments of 200 participants. Statistical analyses will be conducted to relate these measures to the other variables collected by the mobile laboratory. Long-Term Outcomes: We plan to compete for federal grant support for the mobile laboratory in 2025-2026 and anticipate that these longitudinal assessments will be a key component to any successful application.

Year End Progress Summary:
The project met or exceeded both proposed aims during the 2025-2026 reporting period. MC-mLab successfully incorporated longitudinal visits into routine field operations and exceeded the planned ~200 longitudinal assessment target, while biomarker profiling generated biologically coherent signals relevant to neurodegeneration, episodic memory, and processing speed.

Recruitment and cohort growth. As of June 2026, MC-mLab completed 1,831 baseline visits, up from ~1,200 at the start of the grant year. The team completed 276 one-year follow-up visits, exceeding the 200-participant target, and 114 two-year follow-up visits, marking the first time the project reached this milestone. The mobile laboratory is averaging ~65 visits per month and has visited more than 12 cities across Arizona.

Cohort representativeness. The cohort continues to reach populations central to the proposal: 35% of participants reside in rural zip codes, 19% identify as Hispanic/Latino, 15% report a high school diploma or less, 22% report household income ≤$35K, and 30.4% are male.

Specific Aim 1: longitudinal mobile laboratory workflow achieved. Longitudinal visits have been successfully incorporated into the mobile lab workflow. The 276 one-year and 114 two-year follow-up visits demonstrate a mature longitudinal protocol and exceed the proposed target of ~200 longitudinal assessments. The annual follow-up protocol includes repeat cognitive testing, body composition, olfaction, blood pressure, retinal imaging, ultra-low-field MRI, and blood collection.

Specific Aim 2: biomarker assessment advanced. NULISA plasma proteomics using the Alamar NULISA CNS 120-plex panel has been completed on mobile lab participants. NfL (neurofilament light), a marker of neurodegeneration, shows a strong age correlation (ρ=0.649, p=5.9e-132). GFAP (glial fibrillary acidic protein), a marker of astrocyte activation and early Alzheimer's disease biology, also shows a strong age correlation (ρ=0.539, p=9.4e-84). These results support the biological validity of the field-based plasma collection and assay workflow.

Protein-cognition associations. UCHL1 is significantly associated with PAL episodic memory performance (β=-2.19, t=-2.90, p=0.004), and CCL26 is significantly associated with PAL memory (β=-0.53, t=-2.20, p=0.028). CALB2 is significantly associated with processing speed (β=20.2, t=3.33, p=0.0009). These findings identify candidate plasma correlates of memory and speed phenotypes for longitudinal testing.

Genetic and epigenetic profiling. Genome-wide SNP genotyping has been completed using the Illumina Global Screening Array. APOE allele frequencies match the expected population distribution (e2: 8%, e3: 79%, e4: 14%), supporting representative sampling. DNA methylation profiling using Illumina BeadChip technology is underway/completed for the longitudinal cohort.

Cognitive and multimodal validation. Cognitive test results for processing speed/svRT and verbal memory/PAL in the mLab cohort mirror patterns observed in the larger MindCrowd online cohort of ~965,000 participants. Ultra-low-field MRI using the Hyperfine Swoop shows expected age-related patterns, including gray matter volume decline, ventricle expansion, and hippocampal volume decrease, validating portable MRI for field-deployed research.

Retinal, physical, and olfactory measures. Retinal imaging with the Optomed Aurora now includes data on >1,000 participants. Retinal vascular fractal dimension is significantly associated with age, and participants with type 2 diabetes show detectable vessel narrowing independent of age. Grip strength, skeletal muscle mass, and scent detection measured with the 16-item Sniffin' Sticks test all show expected age-related declines.

Collaborations and external visibility. Active collaboration continues with Arizona State University, University of Arizona, and Mayo Clinic - Scottsdale. Three federal NIH grant applications were submitted during the past 12 months.

Challenges. No major challenges were encountered. The longitudinal protocol has been smoothly integrated, and participant retention rates are strong, as evidenced by 276 one-year and 114 two-year follow-up visits. Assurance of high quality retinal imaging is a challenge as immediate feedback on the imaging device isn't indicative of future usefulness of the captured image, this is being addressed via a collaboration with Yalin Wang and team at Arizona State University.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Comparison of transcriptomic changes in AD and FTD in cells with dysfunctional TDP-43.
Kendall Van Keuren-Jensen, PhD, Rita Sattler, PhD. Translational Genomics Research Institute; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Specific Aims:

Aim 1: Improve current methods for detection of CE-containing cells, using samples with a known C9orf72 repeat expansion or GRN mutation, by generating new libraries and increasing sequencing coverage/parameters.
Aim 2: Compare vulnerable cell types in cortex samples from FTD and AD subjects with known TDP-43 pathology and from controls.

Background and Significance:

Detecting cryptic exons (CEs) requires sufficient sequencing depth and coverage across a specific, rare splice junction, a considerably more stringent technical bar than detecting overall gene counts. Because of this, CE detection serves as a sensitive readout for whether our sequencing and library preparation methods are capturing the full transcriptomic complexity of a cell, rather than just its most abundant genes. The same improvements in isolation method, sequencing depth, and read length that allow us to confidently call a CE also give us confidence in detecting long non-coding RNAs (lncRNAs) and other lower-abundance biotypes across all of our single-nucleus sequencing projects.
Beyond this methodological value, CEs arising from TDP-43 loss of function are disease-relevant. The specific cell types in which they originate remain largely unknown. Identifying the cellular origin of CEs is importnat for understanding which neurons and glia are most vulnerable to TDP-43 pathology, and whether the same populations are affected in FTD and AD, two diseases in which TDP-43 dysfunction is common but cell-type specificity is poorly defined. Our prior single-nucleus RNA-seq study of C9orf72 ALS-FTD tissue found CE detection elevated in excitatory neurons, particularly a rare L5 extratelencephalic population similar to von Economo neurons, while glia and interneurons showed comparatively few CE-containing transcripts of STMN2 and KALRN. This finding might be attributed to a low level expression of these genes in glial cells. Determining whether this same vulnerable cell-type signature, or a distinct one, is present in AD will clarify whether TDP-43 dysfunction converges on shared cellular mechanisms across neurodegenerative disease or acts through disease-specific pathways, information essential for identifying therapeutic targets and cell-type-resolved biomarkers of TDP-43 pathology.

Preliminary Data, Experimental Design and Methods:

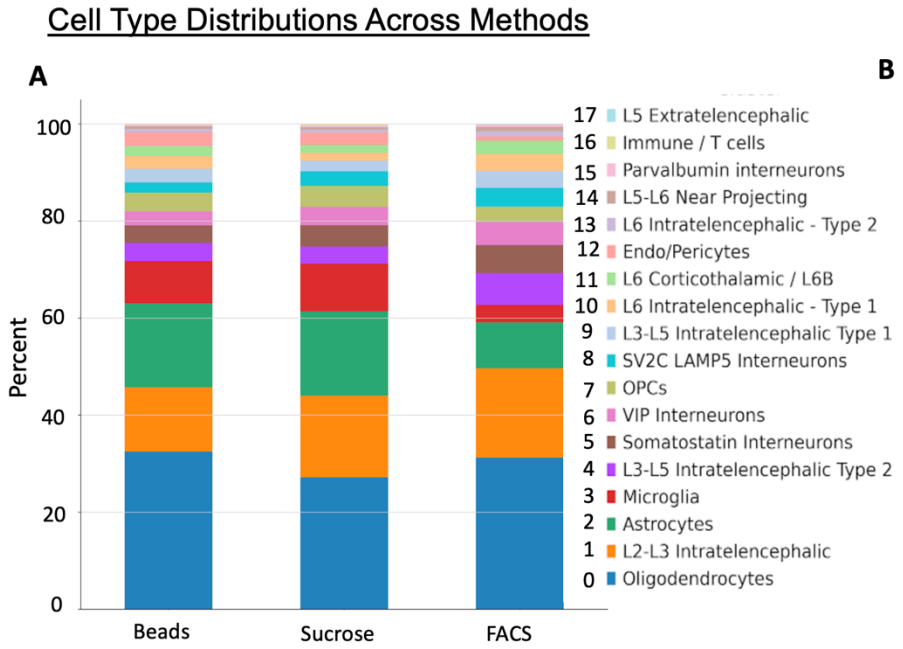
Progress on Aim 1: Improving Transcript Detection Using Cryptic Exons (CE) as a readout

Nuclei isolation method comparison

We piloted three nuclei isolation methods on the same 8 samples (24 total preparations): FACS/sorting, sucrose-gradient separation (performed by Xylena Reed's group at CARD/NIH), and anti-nucleus magnetic bead isolation. All three methods yielded comparable sequencing QC metrics and produced concordant overall cell-type clustering. Comparing cell-type proportions across methods revealed a compositional bias more apparent in FACS-sorted nuclei (Figure 1). Beads and Opti-Prep closely matched one another, FACS detected fewer astrocytes and microglia, but more neurons (colors represent cell types changed by ~1%). The bead-based method gave the most sensitive CE detection across four subjects tested in frontal and temporal cortex, supporting bead-based isolation as a potentially better method going forward.
To further assess the different isolation methods, we compared CE detection across all three isolation methods (FACS, sucrose, and beads) in both frontal and temporal cortex from four

subjects x two brain regions (8 total samples). Beads gave the highest raw CE counts in both regions (124 vs. 54 FACS and 27 sucrose in frontal; 29 vs. 25 FACS and 2 sucrose in temporal). The higher CE burden we detected in frontal relative to temporal cortex is broadly consistent with the frontal-predominant pattern classically associated with behavioral-variant FTD and with neuropathological staging schemes that place frontal cortex TDP-43 pathology at relatively early stages, however, this is not a universal rule.

Notably, sucrose, despite matching beads for cell-type composition, was markedly less sensitive for CE detection. This method had difficulty in detecting CEs in temporal cortex across all four subjects. Nuclei beads appear to be better suited to transcript detection as evidenced by CE counts.



B

Cluster	Beads	Sucrose	FACS
17	0.07	0.1	0.13
16	0.1	0.18	0.04
15	0.27	0.39	0.44
14	0.58	0.47	0.89
13	0.72	0.63	1.07
12	2.78	2.57	0.88
11	2.07	1.57	2.71
10	2.62	1.65	3.54
9	2.82	2.19	3.47
8	2.11	3	3.91
7	3.85	4.33	3.06
6	2.91	3.78	4.81
5	3.64	4.39	5.74
4	3.71	3.57	6.62
3	8.67	9.82	3.58
2	17.36	17.35	9.48
1	13.22	16.82	18.4
0	32.49	27.19	31.24

Figure 1. Cell type distribution across three nuclei isolation methods. A) Stacked bar plot displaying the proportion of each cell type. B) a table of the percentages for each cell type

Long-read sequencing extends CE detection beyond STMN2/KALRN

A key limitation of standard 10x Genomics sequencing is its 3' coverage bias, which causes us to underestimate CE-containing cells for genes whose CEs fall further from the transcript's 3' end. To address this, we sequenced the samples from our Gittings et al 2023 paper using long-read (Kinnex) PacBio. This long-read approach expanded the set of detectable CE-containing genes beyond STMN2 and KALRN to include ATP8A2, CAMK2B, CEP290, HP1BP3, KCNQ2, PPP6R3, RAP1GAP, SEPT7P2, STXBP5L, TRAPPC12, and UNC13A. Combining optimized short-read snRNA-seq (bead isolation) with long-read follow-up sequencing will give us a substantially more sensitive and comprehensive view of CE burden than either method alone.

Progress on Aim 2: Vulnerable Cell Types Across FTD and AD

CE detection in the NOMIS AD cohort

We generated single-nuclei RNA-seq data from the NOMIS cohort (n = 99 subjects spanning the AD neuropathologic change [ADNC] spectrum: 21 Not AD, 14 Low ADNC, 33 Intermediate ADNC, 31 High ADNC) and screened for STMN2 and KALRN cryptic exons as markers of TDP-43 dysfunction, using the same detection pipeline validated in our C9orf72 ALS-FTD spectrum dataset.

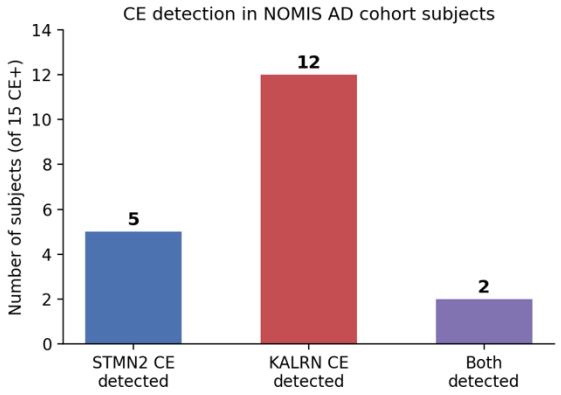


Figure 2. STMN2 and KALRN CE detection in donors with primarily Alzheimer's disease pathology.

CEs were detected in 15 of 99 subjects. In C9orf72-FTD, where STMN2 CEs were the more frequently detected event, in the AD cohort, KALRN CEs were detected more often than STMN2 CEs (12 vs. 5 subjects, with only 2 subjects positive for both; Figure 2). This suggests TDP-43 dysfunction in AD may manifest through different mis-splicing events than C9orf72-FTD.

Deeper characterization of the vulnerable L5 ET population

In parallel, we focused part of our effort toward deeper transcriptional characterization of L5 extratelencephalic (L5 ET) neurons, the rare but selectively vulnerable cluster identified in our C9orf72-FTD work. We expanded our reference annotation to include long non-coding RNAs (lncRNAs) alongside protein-coding genes and reprocessed data from three cortical regions (prefrontal, posterior cingulate, and occipital cortex) in our Alzheimer's disease dataset plus the ROSMAP cohort. This expanded reference did not change L5 ET cluster identity or increase its size, L5 ET nuclei remain a rare population across all regions and cohorts, but it substantially increased the number and diversity of genes detected in these cells, including many lncRNAs not captured by the standard reference (Figure 3). These data indicate that L5 ET neurons are unusually transcriptionally active and complex relative to other cortical neuron types, a property that may relate to their heightened vulnerability to TDP-43 dysfunction.

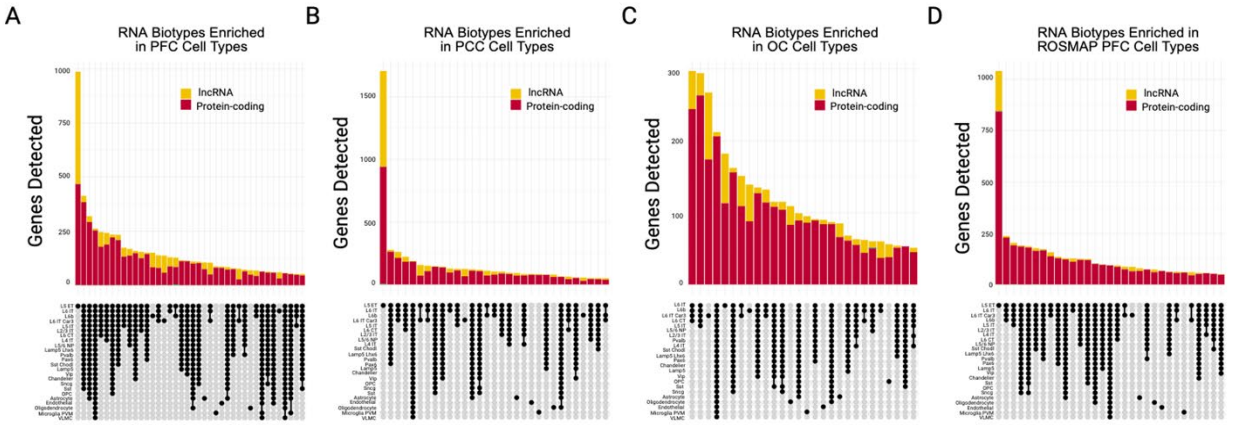


Figure 3. Protein-coding and lncRNAs detected in each cell type by single nuclei sequencing. A) Prefrontal Cortex, B) Posterior Cingulate Cortex, C) Occipital Cortex, D) ROSMAP Prefrontal Cortex. The first cell type in graphs A, B, D is L5 ET and is the most transcriptionally diverse. In C, Occipital Cortex, L5 ETs are not detected.

<u>Proposed One-Year and Long-Term Outcomes:</u>

Over the coming year, we will apply our bead-based isolation protocol and combined short-/long-read sequencing strategy and extend CE screening to build a complete, cell-type-resolved map

of CE burden across the AD neuropathologic change spectrum. We will directly test whether L5 ET transcriptional diversity and lncRNA complexity correlate with CE burden and pathological severity, validate the newly identified long-read CE targets (UNC13A, RAP1GAP, TRAPPC12) at single-cell resolution, and compare CE gene-specificity and cell-type vulnerability between AD and FTD. Because CE detection requires the same depth and coverage needed to confidently resolve lncRNAs and other low-abundance biotypes, these benchmarks will also directly inform the sequencing depth and library preparation standards we apply across our other single-nucleus projects.

Longer term, this work will establish a comprehensive, cell-type-resolved atlas of TDP-43-associated cryptic exon burden spanning the ALS-FTD-AD spectrum, clarifying whether these diseases converge on shared vulnerable cell populations or diverge through disease-specific molecular mechanisms. Identifying cell-type-specific signatures, including the elevated transcriptional and lncRNA complexity we observed in L5 ET neurons, will help define candidate targets for therapeutic and biomarker development. By using CE detection to mark individual neurons undergoing TDP-43 pathology, we can characterize the full transcriptomic signature of these affected cells, rather than relying on the cryptic exon alone. This is particularly valuable because CE-containing transcripts have proven difficult to detect reliably in biofluids. A broader transcriptomic signature derived from CE-marked cells, capturing the fuller range of changes in cells with confirmed TDP-43 pathology, may offer a more robust and accessible route to detecting TDP-43 dysfunction in biofluids. Beyond this specific disease application, using CE detection as a stringent, junction-level readout of transcriptomic depth gives us a generalizable framework for validating sequencing sensitivity and biotype coverage, one we expect to apply beyond this project as we adopt lncRNA-expanded references and long-read approaches elsewhere in the lab.

Year End Progress Summary:

This project set out to (1) improve detection of TDP-43-associated cryptic exons (CEs) in single-nucleus RNA-seq data using existing C9orf72 and GRN samples, and (2) apply that improved method to compare CE burden and vulnerable cell types in AD and FTD. This builds on our recent report of the first single-cell detection of STMN2 and KALRN CEs in C9orf72 ALS-FTD tissue, which also identified the rare L5 extratelencephalic (L5 ET) neuron population as disproportionately enriched for CE-containing cells and transcriptomically similar to von Economo neurons selectively lost in C9orf72-FTD (Gittings and Alsop et al, 2023).

We have pursued two complementary strategies to improve detection under Aim 1. First, we piloted three nuclei isolation methods (FACS, sucrose, and magnetic bead separation). We found that FACS resulted in a different cell distribution compared to beads and sucrose: fewer astrocytes and microglia but higher neuronal populations. Second, to address the 3' coverage bias inherent to short-read 10x Genomics sequencing, we generated long-read (Kinnex) data on samples using PacBio and expanded the number of detectable CE-containing genes beyond STMN2 and KALRN. We detected CEs in ATP8A2, CAMK2B, CEP290, HP1BP3, KCNQ2, PPP6R3, RAP1GAP, SEPT7P2, STXBP5L, TRAPPC12, and UNC13A.

In parallel under Aim 2, we assessed CEs in AD tissue, data were generated using our older methods. We can detect STMN2 and KALRN CEs in AD single nuclei data. We also expanded our reference annotation to include more lncRNAs to assess whether they contributed additional information about disease-state changes in cell populations, and found that vulnerable L5 ET populations had substantially greater transcriptional diversity than previously appreciated. We advanced both aims, refining detection sensitivity using CE junctions as a stringent readout of transcriptomic depth a benchmark that, beyond TDP-43 biology, gives us confidence in our ability to detect lncRNAs and other low-abundance biotypes more broadly, and lays the groundwork for using CE-marked cells to characterize the fuller transcriptomic signature of TDP-43 pathology.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Mapping Expression Quantitative Trait Loci in the Middle Temporal Gyrus of Alzheimer's Disease and Cognitively Normal Controls. Ignazio Piras, PhD. Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

The goal of this project is to identify causal loci associated with Alzheimer's Disease (AD) through expression quantitative loci trait loci (eQTL) mapping and colocalization analysis. The transcriptomics and SNPs data were generated under the R01 AG072643-01 NIH award, which focuses on the mechanism of NPTX2 resilience. The same dataset will be leveraged to conduct an AD-focused analysis. Data and results will be shared on the Accelerated Medicine Partnership - AD (AMP-AD) repository. The study will be carried out in one specific Aim.

Aim 1. eQTL mapping in the Middle Temporal Gyrus (MTG) of AD and Cognitively Normal Controls

1. SNPs and transcriptomics case-control analysis. We will conduct a GWAS using SNPs data, both at the variant and gene level, to detect genomic regions and variants associated with AD. Due to the limited sample size, the results will be cross-referenced with large, independent GWAS datasets. We will also conduct a case-control transcriptomic analysis, complemented with coexpression networks and key driver analysis, in order to prioritize AD-associated genes. Additionally, gene expression will be correlated with neuropathological variables (Braak stage and amyloid plaques), and with a combined AD-neuropathological score.
2. We will conduct an eQTL analysis using the matched SNPs and transcriptomics data, using an interaction model to assess differential patterns of regulation between AD and ND. Genomic regions will be prioritized by cross-referencing the GWAS and case-control transcriptomic studies.
3. We will conduct colocalization analysis on the prioritized genes to assess whether GWAS and eQTL signals share common AD-causal variants.

Background and Significance:

This project aims to identify causal AD loci by combining eQTL mapping with colocalization analysis. It will use an existing dataset of 500+ donors (neuropathologically confirmed AD cases and non-demented controls) originally generated under NIH award R01AG072643-01 (a study of NPTX2-mediated resilience), repurposing it for an AD-focused analysis of the middle temporal gyrus, a region affected early in AD. The goal is to reveal regulatory mechanisms underlying AD and help identify new therapeutic targets.

Preliminary Data, Experimental Design and Methods:

After quality controls, the dataset consisted of 204 AD and 323 ND. The disease status was determined by clinical assessment and confirmed neuropathologically at autopsy. Differential expression analysis was conducted using DESeq2, adjusting for sex, age at death, RIN, post-mortem interval, sample source and sequencing run. After adjustment for multiple testing, we detected a total of 3,217 differentially expressed genes (DEGs). The same samples were genotyped using the Illumina Global Screening Array.

Proposed One-Year and Long-Term Outcomes:

Describe proposed one-year and long-term outcomes.

One-year outcomes. We plan to conduct a more in-depth analysis of the differential expression, complemented by functional pathway analysis, coexpression and key driver analysis, to determine transcriptomics associations with AD in MTG. Then, through eQTL and colocalization

analysis, we will identify causal genetic variants associated with AD through changes in gene expression and in regulatory mechanisms. Finally, data will be shared via the AMP-AD platform, ensuring the dataset will be used by the research community to accelerate AD research efforts.
Long term outcomes. The identification of eQTLs and colocalized variants will provide insights into the molecular pathways associated with AD, advancing our understanding of the disease mechanism and helping to clarify the functional significance of previously identified GWAS loci. Additionally, the prioritized loci will be further investigated as target for drug repositioning and development

Year End Progress Summary:

We investigated patterns of genetic regulation driving the AD transcriptomic signatures using eQTL analysis. We conducted *cis*- and *trans*-eQTL analysis with *Matrix-eQTL* in a matched subsample with both transcriptomics and high-density SNPs data (AD = 199, CTL = 273), detecting a total of 160,512 *cis*-eQTLs (BHP < 0.05) located in 2,438 genes, and 3,333 trans-eQTL ($P < 1.0 \times 10^{-12}$) located in 7 distinct genes. We found an overlap of 64 eQTL genes across the AD vs CTL DEGs. However, we did not observe significant statistical enrichment (BHP = 1.000). These genes were mostly enriched for ECM-related gene programs, overexpressed in AD. These results suggest that the AD-related transcriptional programs are not broadly driven by common regulatory variants in the MTG and may instead reflect disease-state responses and cellular composition changes, with genetic influence affecting only a small proportion of genes. This limited global eQTL enrichment among the DEGs is consistent with other post-mortem brain bulk transcriptomic studies, where the AD-associated signatures primarily reflect disease-state response rather than genetic regulation. Previous studies found the limited genetic influence associated to microglial genes; here, we instead highlight the ECM as a primary target of genetic regulation in the MTG, suggesting that while immune and neuronal signatures may be largely reactive, the structural remodeling of the ECM may be influenced by the individual genetic background.

Given the limited genetic contribution to the AD transcriptional signature, and the lack of the shared eQTL and trait signal required for colocalization, we further characterized the regulatory architecture of the AD transcriptome using coexpression (MEGENA) and regulon (SCENIC) analysis. Coexpression analysis identified three disease-associated modules: a neuron-mitochondrial module suppressed in AD (M5; GABRB3), a microglial immune module upregulated in AD (M6; FCER1G), and an astrocyte-vascular ECM module increased in AD (M8; TAGLN). We further investigated regulon activity changes between AD and CTL, detecting 18 regulons with differential activity. The top regulons with higher activity in AD, accompanied by differential expression of the TFs, were ETV4(+) (LFC = 0.462; BHP = 3.3×10^{-5}; n = 26 genes) and MSX1(+) (LFC = 0.391; BHP = 2.8×10^{-4}; n = 106 genes). The top regulons with lower activity in AD were FOSB(+) (LFC = −0.319; BHP = 3.6×10^{-03}; n = 136 genes) and EGR3(+) (LFC = −0.315; BHP = 4.13×10^{-03}; n = 526 genes). Eleven of the TFs were also differentially expressed in AD vs CTL, including those associated with the top four regulons. Cell Set Enrichment Analysis showed significant enrichment of neuronal and astrocytic genes among the THRB(+), EGR3(+), BCL11A(+), LHX6(+), FOSB(+), and MSX1(+) regulons, consistent with disruption of neuronal-dependent regulation and glia remodeling.

Interestingly, although none of the regulons were significantly enriched for eQTLs, 63.6% of the TFs were also significant cis-eQTL targets, including the synapse-related MSX1(+) (BHP = 0.041) and LTF(+) (BHP = 4.0×10^{-10}), the ECM-related SOHLH2(+) (BHP = 2.36×10^{-15}), and the immune-related ZBTB16(+) (BHP = 0.012). Notably, the coexpression modules associated with AD were strongly enriched for regulon targets: neuronal regulons (THRB(+), BCL11A(+), and EGR3(+)) were preferentially enriched in modules downregulated in AD and associated with synaptic function and excitatory neurons (M5 and related modules), whereas MSX1(+),

POU3F2(+), and ZNF219(+) regulons were enriched in ECM/astrocyte-associated modules upregulated in AD (M8 and M65).

These results support genetic regulation of a subset of regulatory TFs, even though the regulon target sets were not globally enriched for eQTL, confirming what was observed for the DEGs and showing how a limited number of genetic variants can control the large-scale ECM and synaptic remodeling observed in the AD brain. Genetically regulated TFs such as MSX1(+) and EGR3(+) may thereby provide increased susceptibility to the AD disease state.

Publications

Piras IS, Bonfitto A, Song S, Aldabergenova A, Sloan J, Trejo A, Troncoso JC, Geula C, Rogalski EJ, Kawas CH, Corrada M, Beach TG, Serrano GE, Worley PF, Barnes CA, Huentelman MJ. Transcriptomic profiling of the middle temporal gyrus reveals differential glial/neuronal dysregulation across Alzheimer's disease and aging. bioRxiv [Preprint]. 2025 Oct 20:2025.10.19.683343 (submitted to BMC Medicine).

UNIVERSITY OF ARIZONA
PROJECT PROGRESS REPORTS

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Network Imaging and Lifestyle Biomarkers for Evaluating Vascular Contributions to Brain Aging and Alzheimer's Disease. Gene E. Alexander, PhD, David A. Raichlen, PhD, Christian G. Habeck, PhD, Yi Su, PhD, G. Alex Hishaw, MD, Craig Weinkauf, MD, PhD, Theodore P. Trouard, PhD. University of Arizona; University of Southern California; Columbia University; Banner Alzheimer's Institute; Banner University Medical Center; Arizona Alzheimer's Consortium.

Specific Aims:

We plan to address the following specific aims: 1) to determine how PA and SQ relate to network patterns of brain and peripheral body imaging markers of cardiovascular and cerebrovascular health to influence cognitive and brain aging and the risk for AD; and 2) to further develop, evaluate, and apply novel analytic methods for brain and peripheral body imaging to identify robust and reproducible imaging network markers of age-related cognitive dysfunction and AD risk. This proposal will also provide important added value by: 1) further developing and evaluating novel wearable biomarker metrics for the NIA Arizona ADRC Biomarker Core and other Arizona collaborative projects, 2) establishing new analytic tools to support AD research with large-scale datasets across Arizona and nationally, 3) investigating how neuroimaging of key brain structures, i.e., hippocampus and frontotemporal white matter, relate to PA/SQ in older adults; 4) evaluating how PA, SQ, and brain/body imaging networks relate to blood biomarkers of disease, and 5) supporting new external grant proposals on aging and AD risk by Arizona researchers.

Background and Significance:

The older adult population is expected to grow rapidly over the next two decades and it will be critically important to address the associated increase in AD in Arizona and nationally. *APOE* ε4 genetic and cerebrovascular health factors increase the risk for developing AD, whereas engaging in high levels of PA can reduce the risk of AD. Peripheral body imaging may provide novel markers linking differences in PA to cardiovascular and cerebrovascular health with the potential to clarify how lifestyle behaviors influence brain health and the risk for AD. High PA levels have been associated with greater brain volume and connectivity. Studies investigating how differing levels of PA influence brain aging and AD risk are needed. SQ is another important daily activity that can impact brain aging and AD risk. Differences in sleep, as well as daytime sedentary behavior, can influence brain aging and AD risk distinct from PA, and how these different lifestyle behaviors influence each other is not well understood. How these novel approaches can be optimally applied to large-scale datasets to identify robust and reproducible patterns of neuroimaging, peripheral body imaging, behavioral, and blood-based biomarkers have yet to be fully elucidated.

Preliminary Data, Experimental Design and Methods:

We have shown that sedentary behavior is an important factor for brain aging and AD risk, with recent articles published in the *Proceedings of the National Academy of Sciences* and *JAMA* (Raichlen et al., *Proc Natl Acad Sci USA*, 2022; *JAMA*, 2023). We developed a novel multimodal biomarker network analysis, identifying a regional pattern of subcortical brain volume related to a plasma biomarker of cardiovascular risk (Song et al., *Neurobiol Aging*, 2023; *Front Aging Neurosci*, 2024), as well as a neuroimaging pattern of white matter lesion load related to hippocampal volume that were associated with aging (Van Etten, *Front Aging Neurosci*, 2024).

This collaborative, multidisciplinary project proposes to further develop, enhance, evaluate, and apply methods to investigate how brain/body imaging of cardiovascular and cerebrovascular risk relate to lifestyle behavioral metrics of PA/SQ and brain aging and AD. This project will use available large-scale datasets with older adults, ages 45 to 85+, including from the Arizona ADRC, UK Biobank, ADNI, and ARIC. Actigraphy and self-report scales of PA and SQ, brain MRI scans

of structure, function, and connectivity, MRI scans of peripheral body imaging, measures of cognitive function, health status and dementia diagnoses, and available blood biomarkers of AD risk will be obtained from these datasets. The data will be used for analytic method development, testing proposed research questions, and cross-validation across cohorts. This proposal will leverage support from a complementary NIA R01 grant (MPIs: Alexander, Raichlen, Klimentidis) and the NIA ADRC Biomarker Core (Co-Leaders: Ashton, Alexander, Su) to provide access to datasets (Arizona ADRC, UK Biobank, ADNI, ARIC) of clinically well-characterized older adults with MRI scans and actigraphy, differing levels of PA and SQ, dementia and health risk outcomes, and available blood biomarker data.

Proposed One-Year and Long-Term Outcomes:

This proposal will be leveraged to support multiple complementary research projects investigating effects of PA and SQ on cognition, neuroimaging, peripheral body imaging, and blood biomarkers of AD risk. These studies reflect collaborations focused on developing externally funded grant proposals to identify how lifestyle measures of PA and SQ influence cardiovascular and cerebrovascular health to impact brain aging and AD risk. This proposed research has the potential to provide innovative and highly impactful findings for publication on factors that may reduce the risk for dementia and cognitive decline. Importantly, this work will provide critically needed pilot data to support new collaborative, planned proposals for NIH funding, including for our NIA ADRC Biomarker Core competitive grant renewal, a competitive renewal of a currently funded NIA R01 grant on sedentary behavior, and a new NIA R01 application (MPIs: Alexander, Raichlen) on how PA/SQ influence vascular health to impact brain aging and AD risk.

Year End Progress Summary:

We made great progress over the past year with multiple publications using the proposed large-scale and other available datasets in our efforts to advance how different lifestyle behaviors, physical activity, and other health factors impact brain aging and the risk for AD. We demonstrated that several key sleep behaviors, including less than optimal sleep duration, more frequent daytime napping, and greater sleeplessness, were each associated with greater volumes of white matter brain lesions in older adults, supporting these sleep behaviors as having a key role in brain aging and the risk for AD (Ally et al., *Alzheimer's & Dementia*, 2026). This work was also featured in a recent press release, where it received media attention with numerous news outlets. We also had publications showing that chronic inflammation mediates the association between physical activity and telomere length (Ananda et al., *Geroscience*, 2026) and that plasma proteomics can help identify how physical activity influences the risk for dementia (Arani et al., *Medicine and Science in Sports and Exercise*, 2026). We showed how measures of MRI brain age relate to differences in cognitive status in cognitively unimpaired oldest old adults (Britton et al., *Geroscience*, 2025). We used a multivariate network covariance method to identify differences in MRI regional patterns of diffusion of white matter tract integrity related to cardiorespiratory fitness in healthy aging that were associated with cognitive functions in healthy older adults (Smith et al., in preparation). We have shown how associations between sedentary behavior time and cognitive functions in older adults are reflected by non-linear relationships (Maltagliati et al., *Journal of Gerontology: Psychological Science*, 2025). We evaluated the relation between physical activity and sedentary behaviors with cognitive decline, dementia risk and brain structure, showing that these lifestyle behaviors influence cognitive and brain aging (Feter et al., *J Physical Activity and Health*, 2025; *Alzheimer's & Dementia*, in press). Furthermore, we evaluated how cognitive demands and abilities influence the experience of physical endurance, enhancing understanding of the interplay between cognitive function and physical activity behaviors (Aslan et al., *Proc Natl Acad Sci USA*, 2025). As part of an international collaboration, we assisted in the publication of a comprehensive review and perspectives article in *Trends in Neuroscience* providing a proposed taxonomy on how sedentary behavior relates to brain health (Zhang et al., *Trends Neurosci*,

2025). In other collaborative work on the development and evaluation of an approach for evaluating companion dogs living in the community, we helped in the development and evaluation of a set of novel cognitive tasks that are sensitive to age-related dysfunction (Hargrave et al., *Geroscience*, 2026; in preparation), supporting efforts for evaluating cognitive decline in this novel community-based canine model of aging. We have demonstrated that cognitive impairment and the blood-based biomarker, pTau217, are elevated in a vascular cohort of older adults evaluated for vascular disease and that carotid stenosis is associated with processing speed and executive functions (French et al., *Alzheimer's & Dementia*, 2025; Zahra et al., *Alzheimer's & Dementia*, 2025). We have shown that incident dementia is differentially associated with daily lifestyle behaviors assessed over a 24-hour activity cycle, providing a more complete view of how different daily lifestyle behaviors influence dementia risk in older adults (Raichlen et al., *Medicine and Science in Sports and Exercise*, 2025). Furthermore, this work was extended to show that differences in the 24-hour daily activity cycle may be associated with brain aging, as reflected by the volume of brain white matter lesions (Song et al., in preparation). We used a multivariate network covariance analysis to identify a regional pattern of white matter lesion volumes related to cardiorespiratory fitness in healthy older adults, providing a potential marker of cardiovascular brain health (Song et al., submitted). We also found regional brain associations between white matter lesion volume and degree of subjective cognitive complaints in a cohort of older adults with increased risk for AD (Bloom et al., submitted). We have developed a novel cluster analytic approach for combining multiple fluid biomarkers to help identify cognitively unimpaired adults with increased risk for subsequent cognitive decline and dementia, providing the potential for detecting subgroups who benefit most from early interventions (Bharadwaj et al., in preparation).

In addition, the above multiple collaborative results supported by this AAC project have provided important pilot data and findings for our currently submitted and planned grant proposals, including a planned NIA R01 application (MPIs: Alexander, Raichlen) to continue to further investigate how vascular function impacts brain health in the context of aging and how associated lifestyle factors related to PA lifestyle behaviors influence the risk for dementia. The work from this AAC project continues to support our plans for the upcoming competitive renewal of our currently awarded $3.1M NIA grant (MPIs: Alexander, Raichlen, Klimentidis) studying how different types of sedentary behavior impact the course of brain aging and Alzheimer's dementia risk. We additionally re-submitted two collaborative NIH R01 grant applications: 1) to investigate differences in large and small vessel vascular disease in contributing to the risk for AD (PI: Weinkauf; Co-Is: Alexander, Trouard) and 2) to evaluate cognitive decline and dementia in a community-based, companion dog model of aging (PI: MacLean; Co-I: Alexander).

This AAC project has also helped to advance methods for our wearable/digital biomarker research in support of the NIA Arizona Alzheimer's Disease Research Center Biomarker Core (Core Co-Leaders: Ashton, Alexander, Su), for which we submitted our competitive renewal during the past year (ADRC PI: Langbaum). This Biomarker Core provides research access, methodological support, expertise, analyses, and data to Arizona-wide investigators and collaborators nationally for neuroimaging, fluid (plasma, CSF), and behavioral/wearable biomarkers to enhance and support research in AD and brain aging. Work from this AAC project has also continued to provide new methods which complement and support ongoing studies of PA and SQ in healthy oldest old adults that have been supported by the McKnight Brain Research Foundation (MPIs: Alexander, Cohen, Visscher, Rundek) to evaluate how different lifestyle factors influence cognition and brain aging in cognitively unimpaired adults, ages 85+ years. This complementary work is part of ongoing collaborations between investigators at the University of Arizona, University of Florida, University of Alabama, and the University of Miami through the McKnight Brain Institutes.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Understanding Asymptomatic Extracranial Carotid Atherosclerotic Disease Contributions to Blood-brain Barrier Dysfunction. Juan C. Arias, MD, Craig C. Weinkauf, MD, PhD. Division of Vascular Surgery, University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

1. Define the relationship between Blood-Brain Barrier (BBB) dysfunction and aECAD. This aim will evaluate BBB permeability using DCE-MRI, the gold standard in BBB evaluation. We hypothesize that subjects with aECAD will have greater BBB permeability compared to subjects with no aECAD. Determining whether aECAD is a risk factor for BBB dysfunction is important because surgical interventions for treating aECAD exist, but they are not offered for cognitive dysfunction prevention.

2. Evaluate regional specificity of BBB integrity in participants with aECAD. This aim will take advantage of the spatial resolution offered by DCE-MRI to explore specific brain regions susceptible to BBB dysfunction driven by aECAD.

3. Validate our lab's in-house blood-based biomarkers of BBB integrity against DCE-MRI. Our lab is committed to perform a holistic evaluation of the BBB. As such, we are testing additional novel blood-based biomarkers of BBB integrity that provide extensive information of cellular components of the BBB. Performing DCE-MRI will allow us to validate the accuracy of these novel blood-based biomarkers at detecting BBB dysfunction; and more importantly, choose promising biomarkers for clinical translation.

Background and Significance:

BBB dysfunction is recognized as an early step in the development of AD.[1] BBB integrity is dependent on vascular endothelial cells, pericytes, astrocytic end-feet, neurons, and microglia.[2] In recent decades, PDGFR-β has positioned itself as a reliable fluid biomarker of pericyte injury and surrogate marker of BBB dysfunction.[3, 4] Pericytes play a major role in capillary contractility, regulating cerebral blood flow.[5-7] Unfavorable conditions such as hypoxia increase pericyte shed of PDGFR-β, occurring over periods of high stress or death.[3] Driven by hypoperfusion, ischemia, and subsequent hypoxia, increasing evidence supports that aECAD, a cerebrovascular disease with a 20% prevalence in subjects aged 30 to 79 years, [8] is associated with BBB dysfunction.[9] aECAD is defined as an atherosclerotic plaque built-up at the common carotid artery and internal carotid bifurcation that narrows the artery lumen, decreasing blood supply to brain.[10] Patients who have no recent history of stroke or transient ischemic attack (TIA) in the previous six months are deemed "asymptomatic".[11] Surgical removal of the atherosclerotic plaque is offered when stenosis reaches 70%.[11] While current surgical treatment of aECAD is directed towards stroke/TIA prevention, mounting data from small clinical trials indicate that it mitigates cognitive dysfunction.[12-14] Published literature does not support a direct link between pericyte injury and aECAD; however, growing preclinical data suggest that aECAD increased BBB permeability, inflammation and decreased endothelial tight junctions in mice who underwent bilateral carotid ligation compared to mice who received sham surgery.[15, 16]

Preliminary Data:

Our interest in understanding aECAD contributions to preclinical stages of AD pathogenesis, such as BBB dysfunction, has led us to explore associations between carotid stenosis severity and serum PDGFR-β. We found that our patients with aECAD have elevated expression of PDGFR-β.

Experimental Design and Methods:

Study Population: 30 participants enrolled in the prospective Carotid and Mind (CAM) clinical study will be asked to undergo further testing for this proposal. **MRI Data Acquisition:** Participants will undergo a brain MRI in a 3T Siemens Magnetom Skyra with a 32-channel head RF coil available at the UA Translational Bioimaging Resource facility. 3D Saggital T1-weighted MPRAGE (voxel size = 1 mm isotropic) and 3D saggital T2-weighted SPACE (voxel size = 1 mm isotropic) pulse sequences will be used to generate high-resolution segmentations of the brain. Blood-brain barrier (BBB) permeability will be assessed using dynamic contrast-enhanced MRI. Participants will be injected 0.2 mL/kg of Prohance at 2 mL/second intravenously via injection pump. Prior to contrast injection, two 3D fast-spoiled gradient-echo (FSPGR) (voxel size = 1x1x4 mm^3) acquisitions at flip angles 2° and 12° to enable the calculation of pre-contrast longitudinal relaxation times (T1 maps). An intravenous bolus injection will administer simultaneously with the start of 20 acquisitions with 12° flip angle and a temporal resolution of 73 seconds, leading to a DCE-MRI duration of approximately 24 minutes as described by Heye et al.[17]

Data processing: Brain segmentations will be performed using the FreeSurfer image processing suite using both T1-weighted MPRAGE and T2-weighted SPACE[18] The brain blood barrier permeability will be evaluated using K^{trans} values from DCE data and the approach proposed by Heye et al,[17] consisting of a time series scheme that allows to calculate the rate at which the contrast agent moves from the vascular compartment into the tissue compartment, following the Patlak model of tracer leakage.[19] Segmented regions of interest from the Desikan-Killiany atlas generated by FreeSurfer[20] will applied to K^{trans} maps to generate regional BBB permeability statistics. **Statistical analysis:** We will utilize univariate and multivariate analyses to assess the relationship between global and regional BBB permeability and aECAD as described in the approved project proposal. Spearman's rank correlation coefficient or Pearson's correlation coefficient, as appropriate, will be calculated for K^{trans} values and percent carotid stenosis. Regression analysis will further examine this association adjusting for age, sex, incomplete circle of Willis and other relevant confounding factors. Regional BBB permeability analyses will examine K^{trans} mean values in individual brain hemispheres ipsilateral and contralateral to the carotid artery with highest percent stenosis; similar approach to laterally will be applied to vascular territories including the anterior, middle, and posterior cerebral arteries as well as AD signature domain and DMN-associated regions. The validation of serum PDGFR-β and another in-house blood-based biomarkers of BBB integrity against the gold standard DCE-MRI will follow an analogous strategy employing univariate analysis and regression models.

Proposed One-Year and Long-Term Outcomes:

One-year outcomes: Study participants will undergo contrast-enhanced MRI evaluation, data will be processed and analyzed. We hypothesize that aECAD severity will correlate with BBB dysfunction in a series of aECAD-signature regions. **Long-term outcomes:** R01 submission for evaluation of cerebrovascular and blood-brain barrier integrity contributions to Alzheimer's disease risk.

Year End Progress Summary:

For this proposal, a total of 50 participants enrolled in the CAM study were asked to come back for an extra contrast-enhanced MRI. Of those, 34 subjects accepted and came in for imaging. We faced some challenges imaging these patients because the 3T Siemens Skyra scanner was out of service for a few weeks between October and September of 2025. The problem was a drop in Signal-to-Noise in acquisitions that use a multi-band acceleration secondary to a malfunction of the transmitter electronics box that had gone unnoticed for several months. This motivated us to perform a preliminary analysis of the images collected on 15 patients as of late October. Images passed a quality control evaluation and underwent processing as described in the methods

section. A preliminary analysis did not suggest the transmitter electronics box failure affected the integrity of our data as our protocol does not use multi-band acceleration. Moreover, these preliminary results show that Ktrans in the whole brain gray and white matter have a positive correlation with carotid stenosis severity; the correlation is stronger on the hemisphere ipsilateral to the carotid artery with greatest stenosis. We also found a positive correlation between Ktrans in both whole brain gray and white matter with PDGFR-B and Angiopoetin-2 (ANGPT2), which are known blood-based biomarkers of BBB breakdown. While these results are preliminary, they suggest that aECAD is associated with increased BBB permeability, and blood-based biomarkers are a promising screening tool for BBB breakdown. In our quest to explore fast BBB imaging techniques with potential for translation to the clinical setting in collaboration with Dr. Maria Altbach, we compared DCE-MRI to T1Maps-MRI, collected as part of the CAM protocol, finding a moderate to strong association between DCE-derived Ktrans and T1Maps-derived delta maps. While the recommended DCE-MRI acquisition takes 20 minutes of continuous scanning, the T1Maps approach requires acquiring one pre- and one post-contrast scans 20 minutes apart; this allows for scanning in between both scans. Each scan has an acquisition time of 2 minutes and 48 seconds, then the post-contrast images are subtracted from the pre-contrast images, generating the delta maps. Although more testing is needed, delta T1Maps emerge as a promising and efficient alternative to evaluate blood-brain barrier integrity with the potential for clinical translation. These data were accepted for an oral presentation at 2025 International Blood-Brain Barriers Society meeting in Barcelona, Spain. Resulting from attending this conference, we were fortunate to meet and establish a collaboration with Dr. Walter Backes from the Netherlands, an expert in the field of DCE imaging and blood-brain barrier studies. He has provided feedback to our imaging protocols and helped us refine our pre- and post-processing pipelines. At the moment, we have imaged 34 subjects and are currently processing their images according to Dr. Backes recommendations. Results will be share in the 2026 AAC annual meeting in Tucson, Arizona.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Direct comparison of high density recording devices for optimizing isolation of the largest numbers of hippocampus neurons. Carol A. Barnes, PhD, Stephen Cowen, PhD, Matt Huentelman, PhD, Paul Worley, PhD. University of Arizona; Translational Genomics Research Institute; Johns Hopkins University; Arizona Alzheimer's Consortium.

Specific Aims:

To compare hippocampus cell yield performance of tetrode versus neuropixel 2.0 recording probes, to motivate the method we will use for an upcoming RO1 competitive renewal grant.

Background and Significance:

The grant that we are preparing to submit for a competitive renewal is focused on the NPTX2 "resilience mechanism" in the brain. The effect of aging on the human brain shows wide individual variation ranging from early onset Alzheimer's disease (AD) to maintenance of cognitive clarity into the 10th decade. The challenge is to understand why aging can have such disparate outcomes, and why it contributes so profoundly to the risk of neurodegenerative disease. We have examined aging and AD from the perspective of molecular pathways that underlie memory consolidation and determined that a gene termed NPTX2 provides an important clue to human cognitive failure. NPTX2 is expressed by pyramidal neurons and secreted at their excitatory synapses on parvalbumin (PV) interneurons to control inhibitory circuit function. NPTX2 and markers of PV function are prominently down-regulated in the brain of humans with AD, and CSF levels of NPTX2 correlate with both disease state and cognitive performance. NPTX2 is not down-regulated in the brains of individuals who maintain cognitive clarity despite amyloid accumulation (asymptomatic AD) (Xiao et al., 2017). These and other findings support the hypothesis that NPTX2 is associated with brain resilience critical for cognition and fails in the shift from healthy to unhealthy aging. One Aim of the new RO1 proposal involves the use of a rat genetic model for conditional deletion of NPTX2 in a transgenic APP/PS1 AD model (TgF344-AD) that we have created during the awarded grant. One goal of the renewal is to do include high density electrophysiological recordings of hippocampus subregions CA1 and CA3 to determine how NPTX2 loss of function impacts circuit function and behavior. Our prediction is that disrupting the NPTX2 resilience mechanism will accelerate cellular dysfunction and behavior disruption in these rats. For the recording study we want to propose the strongest method of electrophysiological sampling. Because tetrode versus neuropixel recordings have never been examined with the goal of determining which method will provide the highest cell yield, this pilot experiment will allow us to have the data to support our choice of recording method.

Preliminary Data, Experimental Design and Methods:

We are requesting funds to purchase the neuropixel 2.0 probes, cabling and headstage to interface with the data acquisition system before so that we can make the direct tetrode versus neuropixel comparison. Cowen is using the neuropixel 2.0 in his laboratory now, and Barnes is using the hyperdrive tetrode recording device, so that we are prepared to do this direct comparison.

Proposed One-Year and Long-Term Outcomes:

We will conduct the experimental comparison, and use these data for the rationale for the recording approach proposed in Aim 3 of a competitive RO1 renewal of the *NPTX2: Preserving memory circuits in aging and Alzheimer's disease* grant.

Year End Progress Summary:

The goal of this study was to compare two leading technologies for measuring the activities of ensembles of 'spiking' neurons that will be used for planned studies on NPTX2 "resilience mechanism" in the brain and AD. The choice of approach is important as the recording technology impacts the time, cost, nature, and quality of data acquired. Furthermore, different scientific questions are better suited to one approach vs. another. As context, our research investigating aging and Alzheimer's disease involves the measurement of neural activity in the hippocampus to determine how AD and aging impact navigation and memory-associated activity.

Data summarized here comes from the Barnes (tetrodes) and Cowen (Neuropixels probes) labs. Tetrodes have been used for over 40 years and consist of 4 small 13uM wires wrapped together. 12-16 independently moveable tetrodes (4*16 = 64 wires or channels) are typically placed in a 'hyperdrive' that is then implanted above the hippocampus. Extracellular activity is measured from each wire and 'spike sorting' procedures isolate individual cells from the measured waveform and firing rates. Neuropixels probes (NPPs), in contrast, were only recently introduced (2018) and consist of >5000 recording sites spread across 11 mm (vertical depth) providing an unprecedented channel count. NPPs are limited, however, in that they 1) typically are not moveable so one cannot optimize positioning over days to maximize cell count, and 2) only have 4 shanks across the ML or AP axes and so there are fewer independent wires passing through a given region such as the hippocampus. Thus, it was not clear which of these two approaches would be best suited for our scientific questions.

To compare these approaches, we used a combination of recently collected data and legacy data to determine the yield of each method. The measures analyzed were:

Neurons per session:

This measure is ideal for situations when you need to look at interactions between neurons in real time. This is quite important if dynamics are being studied. For example, does spatial novelty enhance between neuron correlations as measured by cross-correlograms?

Total acquired neurons per experiment:

This measure is most important if one is trying to estimate a property of neurons that can be measured independently (e.g., mean firing rate, spatial information content). For example, high values here would be optimal for questions such as 'is the mean firing rate of neurons in the aged CA3 region higher than in young animals?'.

Daily cell counts from a representative sample of experiments

Day	Probe Type	Brain Region	Cell Count
1	Neuropixels	Hippocampus	41
2	Neuropixels	Hippocampus	22
3	Neuropixels	Hippocampus	83
4	Neuropixels	Hippocampus	72
1	Neuropixels	mPFC	390*
2	Neuropixels	mPFC	50
1	Tetrodes	Hippocampus	20
2	Tetrodes	Hippocampus	66
3	Tetrodes	Hippocampus	60
4	Tetrodes	Hippocampus	70
5	Tetrodes	Hippocampus	40

* high due to the long DV extent of mPFC

Mean Counts Per Session (day) Hippocampus only (n = 11 rats for tetrodes, n = 6 rats NPPs)

Hippocampus	Max	Min	Mean
Tetrode	66	4	22.9
Neuropixels	83	16	22

Total est. unique cells per rat across all days (tetrodes = 30 days 8 rats, NPPs = 14 days, 4 rats).

Hippocampus	Max	Min	Mean
Tetrode	714	68	324.63
Neuropixels	150	60	80

Table 1: Results from comparison of tetrodes vs. NPPs.

Results:

Table 1 summarizes measures described above. We found that both tetrodes and NPPs yielded similar cell counts on a given recording session; however, estimates of the total number of unique neurons acquired per animal was higher with tetrode recordings. Acquiring these larger numbers did require more time after each recording session spent adjusting tetrode depth and more recording days. Performing the above experiments identified important and less quantifiable advantages and disadvantages of NPPs and tetrodes. What follows are guidelines based on these observations:

If data acquisition time is limited to < 3 weeks: Choose Neuropixels.
If a daily recording session or the total number of recording sessions are limited (e.g., 2 hrs/day or there is only time to record for 2 weeks/animal), then Neuropixels are optimal. Tetrodes require considerable adjustment before or after each recording session which can add at least 30 minutes to individual sessions. Further, the benefits of the increased total number of unique cells with tetrodes are limited if experiments are time-limited to ~2 weeks. Since NP probes do not require adjustment and have a large but stable cell count, they win if this is the constraint.

If you wish to maximize unique cell count across a 3+ week long experiment: Choose Tetrodes.
If considerable time per animal can be dedicated to recording, then the ability to independently move each tetrode over sessions results in more unique cells relative to NPPs. This does require more time per session and more sessions. In contrast, cell yields from NPPs diminish across days due to gliosis and other factors.

If precise estimation of anatomical location of each site is required: Choose Neuropixels.
NPPs are fixed in place and can be stained using DiI for precise anatomical localization. Furthermore, analysis of LFP (current source density)/single unit signals can be used to precisely identify cell layer.

If you wish to track the activity of individual neurons across days: Choose Neuropixels.
Given the high channel count and the fact that NPPs are fixed, it is possible to confidently track the activity of individual neurons for ~7 days. This is more difficult with tetrodes as tetrodes are typically moved after each session to maximize cell yields.

If a goal is to minimize cost: It depends. Making tetrode arrays is labor and time intensive. If a professional is hired to do this, then the cost is on par with NPPs (~$2300/probe). If, however, labor is ‘free’ (e.g., graduate students), then tetrode arrays are less expensive.
In summary, experiments and analyses supported by ACC were important as they informed the design of planned experiments. For example, given that some experiments by Dr. Cowen involve the analysis of theta and ripple oscillations, the capacity to localize currents with NPPs is a great benefit.

Grant Applications: These data were important for our final 2-year renewal for our R01(NIA **RF1AG081767**) which we received in June. Furthermore, the results have guided the design of the NPTX2 experiment described in the proposal and the approaches planned for the aims of a fall 2026 NIA grant submission.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Microbiome modulation of vagal afferent signaling. Carol Barnes, PhD, Katalin Gothard, MD, PhD, Mario Romero-Ortega, PhD, Emily Cope, PhD, J Gregory Caporaso, PhD. University of Arizona; Northern Arizona University; Arizona Alzheimer's Consortium.

Specific Aims:

To further understand the functional role of microbiome-derived signaling through the vagus nerve in aging and Alzheimer's Disease, we propose the following Specific Aims:

- **Specific Aim 1** (UA). Develop the technology to manipulate the gut and measure resulting vagal nerve outcomes.
- **Specific Aim 2** (supported through NAU funds). To determine what microbiome metatranscriptomic and metabolomic features are associated with vagal nerve activity.

Background and Significance:

Disruptions to the gut microbiome-brain axis have been linked to a range of diseases and disorders affecting brain, including anxiety and depression,[21] Parkinson's disease,[22] autism spectrum disorder,[23] and Alzheimer's disease (AD).[24] The emerging role of the gut microbiome in modulation of neurotransmitters has garnered recent attention, and there is appreciable evidence that select microbiota in the gut produce GABA,[25] norepinephrine,[26] dopamine,[27] and serotonin/serotonin precursors.[28,29] In addition to synthesizing neurotransmitters, gut microbes produce a variety of metabolites, such as short-chain fatty acids and bile acids, that can activate enteroendocrine cells, which in turn form synaptic connections with the vagus nerve.[6] Understanding how gut-derived signals are transmitted to the brain is therefore essential for identifying the mechanistic links between the microbiome and neurological health.

Preliminary Data, Experimental Design and Methods:

With support of the AAC, we have recently published a study that demonstrated unique temporal gut microbiome signatures in 3xTg-AD mice and genetic controls (WT).[11] Three statistical approaches used in this study (ANCOM, Random Forest machine learning, and volatility analysis) demonstrated increased relative abundance in *Bacteroides* in 3xTg-AD mice. Using shallow shotgun metagenomics, which allows for higher taxonomic resolution over amplicon sequencing, demonstrated the presence of several *Bacteroides* species, including *B. fragilis* in 3xTg-AD mice. Next, we supplemented mice with *B. fragilis* monthly for 52 weeks and observed consistent and early colonization of *B. fragilis* in 3xTg-AD mice and delayed colonization in WT controls.

This suggested to us that there was a niche available early on in 3xTg-AD mice that allowed for *B. fragilis* colonization. In this study, we also observed an increase in *gfap* gene expression, indicating gliosis, in 3xTg-AD mice not supplemented with *B. fragilis*, as expected. However, when mice were supplemented with *B. fragilis*, *gfap* expression did not increase with age. FDR $p<0.05$). Also of interest, we observed a significant decrease in *slc1a3*, an astrocyte glutamate uptake receptor, in 52-week-old 3xTg-AD mice supplemented with *B. fragilis* compared to 3xTg-AD mice given a sterile vehicle control.

Using untargeted metabolomics, we found that *B. fragilis* modulated several metabolites. For example, *B. fragilis*-treated mice had reduced fecal secondary taurinated bile acids at 8 weeks of age, resembling control mice.

These findings, along with evidence from previous studies, suggest that *Bacteroides fragilis* may exert neuromodulatory effects; however, the underlying mechanisms remain poorly understood.

Proposed One-Year and Long-Term Outcomes:

The data obtained from these experiments will be used to prepare an R01 grant to study not only vagal main trunk nerve activity after microbiome manipulation. Depending on the specific outcome, we will want to propose to record activity first from the nucleus of the solitary tract, which receives afferent sensory input from vagal ganglion cells. If there are clear behavioral differences that arise from *B. fragilis* treatment, we will also propose to record from the amygdala and hippocampus to determine whether the balance of excitatory and inhibitory activity is altered in these structures. We will also use the discoveries made from the metabolomics and transcriptomic studies to predict specific microbial metabolic pathways to manipulate that will impact vagal function. Future studies will also include assessment of aging and Alzheimer's disease rodent models.

Year End Progress Summary:

The overall goal of this project (07/01/25 – 06/30/26) was to determine if we could develop a system that would allow us to directly record activity of the vagus nerve while altering the composition of the microbiota of the gut. This would allow direct experimental assessment of the impact of changing the microbiota on signaling from the vagus nerve to the brain. Inspired by the invention of the "sutrode" electrode by our colleague Dr. Romero-Ortega, which he has used to record activity from other peripheral nervous system nerves, we proposed to use his new electrode design for our exploratory experiments.

Our initial set of experiments aimed to first determine whether we could isolate and record vagal units with the sutrode. This involved learning how to dissect the region around the vagus nerve, and to wrap the sutrode around the nerve without breaking the electrode or damaging the nerve. Dr. Gothard was the primary surgeon for these preparations, guided by Dr. Romero-Ortega and his students and staff. We performed several experiments in these initial stages and did several injections directly into the gut to determine if we could detect any changes in overall firing recorded from the vagus nerve in response to these treatments. The early experiments experienced two main confounding features, namely, high electrical noise in the system, and artifacts from the actual needle poke into the gut for the injections. Students from the Barnes lab were able to improve upon these confounds in later experiments with respect to the injections. This improvement involved creating a chronic duodenal catheterization system that minimized artifacts associated with injections during the duodenal manipulations that included neutral (PBS) and various forms of *Bacteroides* species, to examine the impact that they had on vagus nerve responses. The second issue to overcome was the high levels of background noise in the system, which was resolved to a large degree by the Romero-Ortega lab purchasing a new recording setup with better grounding capabilities. In the early studies we could record 'overall multiunit firing properties', but it was difficult to isolate and identify single vagal nerve responses. With the new recording system, we were able to isolate single vagal action potentials, and through template matching, verify that we were recording from the same cells throughout the experimental treatment components.

Dr. Cope provided us with forms of *Bacteroides* preparations that had been identified as early microbiome colonizers in her AD mouse model (namely, *B. fragilis).* This was our first microbe target for testing the functional impact of changing microbiota content in the duodenum on vagus nerve output. She has found that *B. fragilis* can modulate several metabolites of interest in the gut, and we hypothesized that these may potentially modulate vagal nerve activity. We show an example of data from our last experiment in which we were able to identify clearly separate single

units from the sutrode recording. What is shown in Figure 1 is the average firing of all units during a baseline period, a control period with PBS injection, followed by two sessions of heat-killed *B. fragilis,* then a final session with live *B. fragilis* injection. What can be pointed out from this experiment is that there is quite a bit of variability in the firing rates among these recorded cells, but it appears that there was a decrease in firing that occurred after both the heat-killed injection times, which was even greater after the live injection. Unfortunately, there was also an apparent continual diminution of firing across the entire course of the experiment. Thus, we did not achieve the stability of recordings that we had hoped, making clear interpretation of our results difficult.

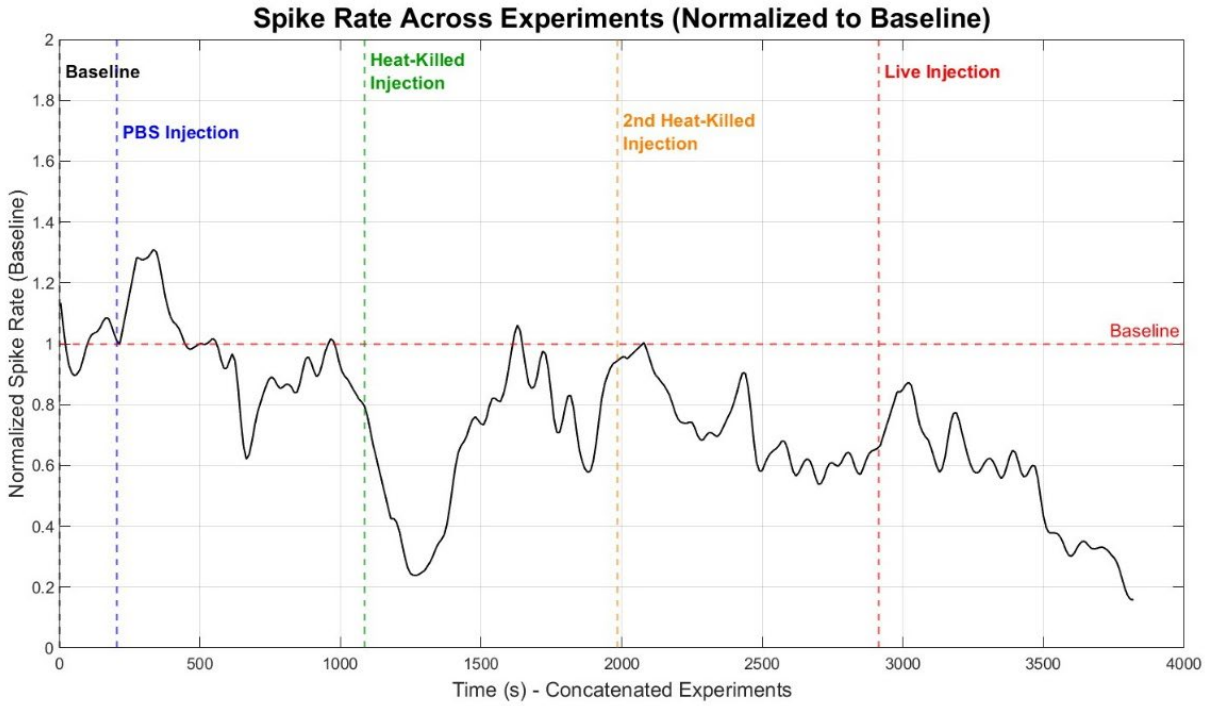


Figure 1. Mean single unit firing activity across time, with intervening control solution and bacterial solution injections.

Because our overall goal was to eventually be able to make this preparation into an awake, freely behaving recording system, the results were somewhat disappointing. First of all, the surgical isolation of the vagus nerve was more challenging than we had anticipated, taking from 1 to 3 hours for successful location and definitive identification, before the sutrode could be wrapped around the nerve for recording. Second, the sutrode itself was quite delicate. It appeared from our experiments that either the sutrode, or the acute preparation itself, may have had a maximum recording duration limited to ≤3 hours. Thus, we now believe it would be difficult to transfer the sutrode method to a chronic recording situation where long-term durability of the recording device would be critical. Finally, while the chronic duodenal catheterization system that was eventually developed did work quite well, functionality of all components of the system would be needed to be realized simultaneously, and it is our judgment that exploration of other approaches will be required for successful completion of the goal of recording vagus nerve activity in awake behaving animals, while manipulating gut microbiome content. We hope to continue to search for a resolution to these barriers, so that we can eventually realize the ability to continuously monitor vagus nerve action potentials during unrestrained behavior, and under controlled treatment applications.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Non-match ISAC Support. Carol A. Barnes, PhD. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

- To provide administrative ISAC support to Dr. Carol A. Barnes, the chair of the ISAC.
- To perform grant application management for the ADRC's Developmental and Pilot Grant programs.

Background and Significance

The Internal Scientific Advisory Committee of the Arizona Alzheimer's Disease Consortium (ADC) is responsible for providing internal governance for the statewide Consortium. This committee has representatives from all seven consortium institutions. The ISAC is responsible for reviewing the progress and coordination of all ADC activities and projects, including approval of state budgets for recommendation to the Board of Directors for funding through the state of Arizona, DHS. The ISAC meets regularly to ensure the proper and productive utilization of state resources and institutional matching funds.

Dr. Barnes serves as Chair of the Internal Scientific Advisory Committee of the Arizona Alzheimer's Consortium and Director of the Ad Hoc Review Program. Dr. Winnie Liang and Trisha Walsh assist Dr. Barnes with the administrative aspects of the development and pilot grant applications for DHS state funding.

Preliminary Data, Experimental Design and Methods:

Not applicable.

Proposed One-Year and Long-Term Outcomes:

The short and long-term outcomes are to facilitate the operation of the Arizona Alzheimer's Consortium Internal Scientific Advisory Committee. Specifically, the Chair assigns reviewers for the pilot projects that may be funded by the state, reads all the grants and all the reviewers' comments, and makes a summary report to the ISAC for discussion. This facilitates the decisions for the submitted grants that may be funded.

Year End Progress Summary:

There were 27 applications received for the Arizona ADRC state and federal development grants, and all were reviewed by Carol Barnes; 26 were complete and eligible for full review and the 13 highest scored applications were reviewed at the ISAC meeting which was held on February 5, 2026. Of the grants presented by Dr Barnes, the following were selected for the Pilot Grant Awards: Yilin Liu (UofA): Title: *Precision Neuromodulation for Cognitive Aging: Leveraging BrainAGE to Predict and Personalize rTMS Response*, Jessica Verpeut (ASU): Title: *Behavioral and blood biomarkers in a preclinical rodent model of Alzheimer's disease* and Ashley Boehringer (ASU): Title: *Spatial Transcriptomics to Assess Gene Expression Changes by Disease State*.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Pathophysiological characterization of the brain's lymphatics in a transgenic rodent model of Alzheimer's disease. Mitchell Bartlett, PhD, Kristian Doyle, PhD, Elizabeth Hutchinson, PhD, Helena Morrison, PhD, Paulo Pires, PhD, Marlys Witte MD. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

Specific Aim 1. Evaluate the hypothesis that cervical lymphatic vessel (CLV) function progressively declines from 3 (pre-), to 6 (early-), to 12-months (mid-stage AD) of age in TgF344AD rats. We will answer the following questions:

1. Does CLV contractility decrease as a function of age?
2. Does a decrease in CLV contractility generate a cycle favoring a pathophysiological accumulation of Aβ, tau, neurofibrillary tangles (NFTs), and other AD-biomarkers.
3. Can we correlate the known cognitive dysfunction in this model with decreased CLV contractility and the accumulation of AD-biomarkers in the brain/cervical lymph nodes?

Specific Aim 2. Evaluate the hypothesis that both glymphatic and meningeal lymphatic vessel (MLV) function declines from 3 (pre-), to 6 (early-), to 12-months (mid-stage AD) of age in TgF344AD rats. We will answer the following questions:

1. Does glymphatic clearance, measured by MRI, decrease with age and is this correlated with a loss of aquaporin-4 channels in the hippocampus and cortex?
2. Using MRI/fluorescent tracers, is MLV clearance impaired and is this correlated with impaired cognitive function and increased AD biomarkers?
3. Does aging result in an increase in Aβ deposits in the MLVs and does this change their structure (*e.g., narrowing of the MLV lumen*)?

Background and Significance:

Mounting evidence implicates that impaired function of the brain's lymphatic system plays a pivotal role in the accumulation of Aβ and the progression of Alzheimer's disease (AD). Clearance of cerebrospinal/interstitial fluid (CSF/ISF), including dissolved macromolecules, like Aβ, follows a complex route that begins with the glymphatic system. Here, CSF is propelled through paravascular spaces by the cerebral microcirculation's vasomotion, before entering the brain parenchyma via aquaporin-4 channels CSF mixes with ISF, containing Aβ, and then follows a convective and diffusive trajectory where it is collected in the paravenous space and transported to noncontractile meningeal lymphatic vessels (MLVs). Both paths follow a unidirectional flow through contractile cervical lymphatic vessels (CLVs), before emptying in their respective cervical lymph nodes (CLNs). Thus, impairments will allow Aβ to accumulate, leading to cognitive dysfunction, and eventually AD. Accordingly, obstructing the MLVs and ligating deep CLVs reduces clearance and increases Aβ accumulation in the brains of AD mice.

A common therapeutic approach to AD has been to reduce amyloid-beta Aβ accumulation. For example, FDA approved monoclonal antibodies (mABs) reduce Aβ aggregation, but only slow cognitive decline in some AD populations, without improving cognition. In addition to their limited efficacy, mAbs are expensive, and have significant side-effects. My current research is focused on the development of novel, translational therapeutics for the treatment of AD that specifically target the CLVs, as there are no therapies that promote the lymphatic clearance of Aβ from the brain. These include developing manual lymphatic drainage (MLD; *previously funded AAC grant; PI: M. Witte*), which we have demonstrated improves cognitive function and reduces AD-biomarkers, and an innovative surgical approach wherein my collaborators and I are repurposing lymphatic reconstructive surgical techniques to aid in bypassing the obstruction of the CLVs that may occur in AD. However, a challenge to developing a new therapy is having an appropriate

animal model of AD. Currently, there is limited information about the pathophysiological changes that occur in the brain's lymphatic pathway of TgF344AD rats. This is a critical gap in knowledge and is necessary to determine therapeutic windows for targeting the brain's lymphatics, which will improve future therapeutic outcomes and precision medicine. The primary objective of Aim 1 is to address these gaps in the TgF344AD rat, which is of additional importance as this model has many advantages over other available rodent AD models. For example, rats are evolutionarily closer to humans than mice, rats express all six tau isoforms present in humans, and specific to the TgF344AD model—it has all 5 major hallmarks of AD.

Preliminary Data, Experimental Design and Methods:
For Aims 1 and 2, male and female TgF344AD/WT rats (n = 8 rats/genotype/timepoint) will undergo behavioral testing at 3 (pre-), 6 (early-), 12-months (mid-stage AD) of age. Following behavior, they will be split into two cohorts for each Aim. In Aim 1, n = 4 rats/genotype/timepoint will be utilized to investigate *ex vivo* contractility in the deep and superficial CLVs, followed by analysis of AD biomarkers via western blot, ELISA, and single molecule array assays. In **Aim 2**, n = 4 rats/genotype/timepoint will have an intra-cisterna magna (ICM) catheter installed and lymph dynamics will be measured by gadolinium (Gd) uptake via MRI. Once Gd has cleared a fluorescent tracer will be injected via the ICM catheter. This will be followed by transcardial perfusion to assess tracer clearance from the MLVs to the cervical lymph nodes, followed by brain collection for immunohistochemistry.

Proposed One-Year and Long-Term Outcomes:
1 Year (**months**): **1-3)** Breed rats for 3/6-mo. timepoints. Behavior testing in bred 12-mo. rats, followed by experiments outlined in **Aims 1**/**2**. **4-6)** Behavior testing and experiments in **Aims 1**/**2** for 3-mo. rats. Complete WB/IHC analysis for 12-mo. rats. **7-9)** Behavior testing and experiments in **Aims 1**/**2** for 6-mo. rats. Complete WB/IHC analysis for 3-mo. rats. **10-12)** Repeat **Aims 1**/**2** experiments for any missing data. Complete remaining WB/IHC or imaging analysis. **Grant Submission:** The AAC grant will support an R01 application (NCCIH NOT-HL-23-099) demonstrating MLD is neuroprotective in 5xFAD mice and an Alzheimer Association fellowship resubmission in September 2025 for Dr. Bartlett.

Year End Progress Summary:
Specific Aim 1. Multiple protocols were developed and optimized to measure the cervical lymphatic vessel function in rodents. First, *ex vivo* myography was developed for measurement in rat cervical lymphatic vessels to measure contractility as a function of age. To determine contractility, the following protocol was developed for rats. Following euthanasia, afferent superficial cervical lymphatic vessels were isolated from mice by microdissection and cannulated onto glass micropipettes. Pressure-response curves were generated by sequentially adjusting intraluminal pressure from 1 to 10 cm H_2O in stepwise increments with 3-minute recordings at each pressure. Measured parameters included contractile frequency, end-diastolic diameter, end-systolic diameter, and ejection fraction. Earlier attempts at myography in mouse models of AD demonstrated a disease-related impairment in vessel contractility. Initial attempts at myography in rat vessels have been demonstrated to be technically successful and data collection is ongoing in the TgF344AD model, with new timepoints being included because of new funding (*see below*). A second protocol to measure cervical lymphatic vessel clearance was also developed with the use of fluorescent and colorimetric tracers injected via an ommaya pump/cannula into the cisterna magna. Following the administration of a tracer into the cisterna magna, TgF344-AD rats show a decreased trend of tracer accumulation in the superficial cervical lymph nodes suggesting impaired lymphatic clearance. Importantly, we can now do these in awake animals, which is a departure from the literature in which tracer studies are done under anesthesia. Additional studies

to determine if this is dependent on the location of the tracer's administration (cisterna magna, brain parenchyma, etc) and a full comparison of the impact of age are ongoing.

Deep and superficial cervical lymph nodes have been collected from the TgF344AD rats at multiple timepoints (3, 6, 9, and 12-months of age) for biomarker analysis. We have optimized the extraction protocol to measure amyloid-beta 40 and 42 using a single molecule array assay and are currently working on quantifying tau in these tissues. We have also developed a collaboration with an expert in neuropathology at Medical University of South Carolina, Onder Albayram, PhD, for future histological analysis of the lymph nodes (*see Publication Section*).

Last, expertise in behavioral testing was acquired and specific tests (novel object recognition, open field, water maze) have been established in this model. These tests are being optimized in our lab to test cognitive function at different timepoints throughout the lifespan of the TgF344AD rat model.

Specific Aim 2. Immunofluorescence and immunohistochemistry studies were conducted to determine whether impaired glymphatic clearance correlates with the accumulation of Alzheimer's disease pathology. Multiplex immunofluorescence staining was developed to quantify aquaporin-4, monomeric and oligomeric amyloid-beta plaques, Type IV collagen-positive vasculature, and nuclei throughout the hippocampus and cortex. Additional staining is being developed for phosphorylated tau (Ser202/Thr205), while Iba-1 is being used to assess microglial density, morphology (ramified vs. amoeboid), and localization relative to plaques. Staining and stereological analyses are ongoing.

Time-series contrast-enhanced MRI using a T1-weighted MDEFT sequence following intracisterna magna gadolinium administration is also being optimized. Preliminary studies in control mice demonstrated visualization of cervical lymph nodes, meningeal lymphatic vessels, and tracer accumulation near the cribriform plate. An MRI-compatible Ommaya reservoir pump is now being utilized to improve tracer delivery and minimize leakage.

Immunofluorescent staining of meningeal tissues has also been established in our laboratory. Following microdissection, successful staining for LYVE-1 and CD31 enabled visualization of lymphatic and endothelial structures. Preliminary findings suggest meningeal lymphatic vessel lumens narrow in TgF344AD rats at later disease stages. Ongoing studies are evaluating these structural changes and developing methods to detect AD-related biomarkers, including amyloid-beta, within the meninges.

Challenges and Highlights. The primary challenge encountered during the project was the breeding and availability of age- and litter-matched TgF344AD rats, partly due to health issues within the colony that have since been resolved through the establishment of new breeding pairs. To mitigate these limitations, 5xFAD and wild-type mice were used to develop and optimize protocols. A secondary challenge was MRI downtime that coincided with the availability of study animals; this was addressed by using mice and control rats to optimize imaging methods and generate proof-of-principle data. The work remains ongoing, and support from the Arizona Alzheimer's Consortium enabled the generation of critical preliminary data, infrastructure, and collaborations that helped launch Dr. Bartlett's transition to independence. **Most importantly, these efforts, supported by the AAC, contributed to him being awarded an NIH/NINDS K99/R00 and multiple smaller grants**. This funding and research also played a role in The University of Arizona receiving its first ever ARPA-H grant and directly provided proof-of concept data utilized in applications to the Alzheimer's Association and Arizona Biomedical Research Centre (ABRC). Dr. Bartlett's letter of intent was selected for further review by the ABRC with a funding decision expected July 1, 2026.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

A Deep Learning Framework for MRI-driven Estimation of Brain Age using Precision Aging Network Data; Ali Bilgin, PhD, Nan-kuei Chen, PhD, Lee Ryan, PhD, Ted Trouard, PhD, Hasan Ozgur, MD, Maria Altbach, PhD. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

The specific aim of this project is to develop a deep learning (DL) framework for estimation of brain age (BA) using Precision Aging Network (PAN) data. The proposed architecture will use Magnetic Resonance Imaging (MRI) data as input and provide an estimate of BA as output. Since the goal is to use this DL framework to study imaging biomarkers of aging, the architecture will be designed to allow the use multi-contrast MRI data as input (e.g. structural T1-weighted MRI, Fluid-Attenuated Inversion Recovery (FLAIR) MRI (for brain tissue abnormalities such as White Matter Hyperintensities (WMHs)), diffusion MRI (for brain tissue microstructure and white matter connectivity), etc.) as well as incorporation of auxiliary information (such as sex or genetic information). It is worth emphasizing that the longer-term goal of the project is not just to develop DL frameworks for accurate estimation of BA, but to be able to utilize such frameworks as a tool to provide neuroanatomic interpretability of aging. As such, we will also incorporate explainable AI (XAI) techniques into this framework to understand the reasoning behind the BA estimate generated by the method (e.g., by using spatial attention maps that will allow us to visualize what regions of the brain in each image contrast had a positive or negative influence on the BA estimate).

Background and Significance:

MRI-based BA estimation uses structural neuroimaging data and machine learning techniques to quantify biological brain aging and identify deviations from typical aging trajectories. The difference between predicted BA and chronological age (CA), known as the brain age gap (BAG), has emerged as a biomarker of accelerated or delayed brain aging. Since the introduction of early frameworks such as BrainAGE, methods have evolved from traditional machine learning approaches to deep learning architectures, resulting in improved prediction of accuracy and generalizability.

BA estimation has gained significant interest due to its associations with cognitive decline, neurodegenerative diseases, and mortality risk. Elevated BAG has been reported in individuals with mild cognitive impairment and Alzheimer's disease, supporting its potential utility as a marker of brain health and age-related neurological changes. These advances highlight the value of BA estimation as a quantitative tool for studying brain aging and disease-related alterations in brain structure.

Preliminary Data:

The USC brain age estimator was evaluated in a cohort of cognitively normal participants and demonstrated good agreement between CA and predicted BA, with mean absolute errors (MAEs) of 2.42 years for males and 2.23 years for females. Saliency map analyses were performed in cognitively normal and cognitively impaired cohorts to identify brain regions contributing to model predictions. Differences in saliency patterns were observed between groups, indicating potential variations in the neuroanatomical features underlying brain age estimation across cognitive states.

Experimental Design and Methods:

Task 1 Baseline Brain Age Estimation: The USC BA estimator will be deployed on the PAN dataset to establish a performance baseline. T1-weighted MRI scans will be processed using FreeSurfer, and BA estimates will be generated for participants older than 21 years. Model

performance will be assessed by comparing BA with CA, with additional analyses planned across sex and MRI acquisition sites to evaluate subgroup variability.

Task 2 Model Development and Enhancement: The original TensorFlow-based USC BA estimator will be reconstructed in PyTorch and validated against the baseline implementation. A training framework will be developed using large-scale neuroimaging datasets available on the compute cluster. Two enhancement strategies will be investigated: (1) incorporation of auxiliary demographic information, including sex, through feature encoding methods, and (2) integration of additional imaging modalities such as FLAIR, white matter hyperintensity maps, and diffusion FA images using multi-channel and multi-branch network architectures. Model performance and interpretability will be evaluated using statistical comparisons and saliency-based visualization techniques.

Proposed One-Year and Long-Term Outcomes:

The results obtained in this project will be used as preliminary data to support the upcoming renewal of the PAN project. Longer-term, ability to combine auxiliary information with imaging data to study the phenotypic age of the human brain is likely to facilitate the development of highly accurate, individualized predictive models that not only forecast the onset and progression of neurodegenerative conditions but also guide tailored intervention strategies.

Year End Progress Summary:

The goal of this pilot project was to establish a DL framework for MRI-based BA estimation using PAN data. During the reporting period, multiple BA estimation pipelines were deployed on PAN data, a baseline model was reimplemented and extended in PyTorch, large-scale neuroimaging datasets were curated for model development, and analyses were initiated to investigate associations between brain age measures, white matter hyperintensity burden, and cognitive aging.

A major first-year outcome was the successful deployment of multiple MRI-based brain age estimation pipelines on PAN imaging data, including USC BA, brainAgeR, and PyMent. BA estimates were generated for all PAN participants with available MRI scans and organized to support future longitudinal analyses as additional participants are enrolled. Comparison of the deployed methods demonstrated MAEs of 4.2 years for USC BA, 5.8 years for brainAgeR, and 3.5 years for PyMent. The resulting BA and BAG measures are being used in ongoing analyses examining relationships with other PAN biomarkers, including white matter hyperintensity burden and cognitive performance.

In parallel, we re-implemented the USC BA model in PyTorch and validated it by transferring weights from the original TensorFlow implementation, confirming comparable brain age predictions. Building on this framework, we developed and evaluated two architectures that incorporate participant-level covariates such as sex: a late-fusion model that combines imaging and covariate features at the prediction stage, and a Feature-wise Linear Modulation (FiLM) model that integrates covariates through feature modulation. These developments establish a flexible platform for future brain age models that incorporate demographic and biological information.

A third major area of progress was neuroimaging data collection and curation. To support brain age model development, we assembled and curated MRI data from multiple publicly available cohorts, including AOMIC, DLBS, MASiVar, TempleSocial, CamCAN, UCLA LA5c, ADNI, IXI, and OASIS-3. Collectively, these datasets comprise 5,010 MRI scans spanning a broad age range and include T1-weighted structural MRI, FLAIR MRI, and diffusion MRI. The datasets have been organized into standardized processing pipelines to support training, validation, and future development of both single-modality and multimodal brain age estimation models.

The data curation and preprocessing effort has been one of the most time-intensive and challenging components of the project. MRI-based brain age estimation requires consistent image

orientation, spatial normalization, tissue preprocessing, quality control, and, in many cases, integration with outputs from tools such as FreeSurfer, ANTs,or related neuroimaging software. The complexity increases further when incorporating FLAIR, diffusion MRI, and derived pathology maps (e.g. WMH maps), because these images often require additional registration, masking, and quality-control steps. These challenges have slowed the rate at which curated training data can be finalized, but the large-scale training data are necessary for building robust models that can generalize across datasets and imaging protocols.

The brain age estimates generated during this pilot period have already supported new scientific analyses. One important finding from our PAN analyses is that WMH burden is associated with BAG independent of age. Specifically, individuals with greater WMH burden tend to show older-appearing brains relative to their chronological age, suggesting that vascular or white matter injury may contribute to accelerated MRI-defined brain aging. We examined this relationship using multiple independent approaches for estimating both brain age and WMH burden. After adjustment for chronological age, sex, imaging site, and total intracranial volume, significant associations between WMH burden and BAG were observed across all analytical approaches ($r = 0.159–0.294$, all $p < 0.001$) and were confirmed in multivariable regression analyses ($\beta = 0.564–1.111$, all $p < 0.001$). These findings indicate that WMH burden provides information about brain aging beyond chronological age alone.

These findings are scientifically important because WMHs are common in aging populations and are associated with vascular risk, cognitive decline, and neurodegenerative outcomes. The observed association with BAG suggests that MRI-derived brain age may capture aspects of accumulated white matter injury and may serve as an integrative biomarker of brain health. The consistency of findings across multiple analytical approaches further supports the robustness of this relationship. This work has generated several tangible research products, including an abstract submitted to the AAC annual meeting and a manuscript currently in preparation. The manuscript will focus on the relationship between WMH burden and MRI-derived brain age gap in the PAN cohort, with additional analyses examining covariates, model dependence, and potential regional or anatomical interpretation.

The project also made meaningful progress toward the proposed long-term outcomes. The current framework is now positioned to support individualized brain age estimation using both MRI data and auxiliary participant information. The PyTorch implementation provides a flexible platform for incorporating additional MRI contrasts, including FLAIR, WMH maps, and diffusion-derived measures. The late-fusion and FiLM-based models establish an initial strategy for integrating participant-level covariates such as sex, and the same framework can be extended in the future to include genetic, cognitive, vascular, or other biological variables. These capabilities directly support the long-term goal of using brain age estimation not only as a predictive tool, but also as a framework for studying neuroanatomic and phenotypic patterns of brain aging.

The pilot project has also strengthened collaborations and created new opportunities for future research. First, the preliminary data and methodologies developed in this project were used for submission of an F32 Postdoctoral Fellowship grant titled “Linking Carotid Plaque Composition to Vascular Contributions in Alzheimer’s Disease and Related Dementias” by Dr. Brian Toner, a postdoctoral associate working with Drs. Bilgin and Altbach. The very good news is that Dr. Toner withdrew this application a few months after the submission, because he has accepted an Assistant Professor position at Florida Atlantic University and is therefore no longer eligible for an F32 award.

We have also initiated an ongoing collaboration with Dr. Ying-Hui Chou’s group, in which our brain age estimation pipelines will be applied to datasets from studies investigating whether repetitive transcranial magnetic stimulation (rTMS) can mitigate cognitive decline.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Cross-Vendor MRI Pulse Sequences for Multi-Scale Alzheimer's Research in Preclinical and Clinical Settings. Nan-kuei Chen, PhD, Ted Trouard, PhD, Elizabeth Hutchinson, PhD, Ashley Stokes, PhD. University of Arizona; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Specific Aims:

1. We will use the open-source *Pulseq* language to implement a suite of advanced MRI pulse sequences that are critical for Alzheimer's research but currently lack cross-vendor support. These pulse sequences include:
   a) pseudo-continuous arterial spin labeling (pCASL) using distortion-free, three-dimensional balanced steady-state free precession (3D-bSSFP) with multiple post-labeling delay times for robust cerebral blood flow mapping;
   b) high-resolution, dynamic diffusion MRI using segmented echo planar imaging (EPI) for measuring perivascular cerebrospinal fluid (pvCSF) dynamics; and
   c) diffusion-weighted pCASL for assessing blood-brain barrier integrity without the need for contrast agents.
2. We will update the existing *Pulseq* interpreter for Bruker MRI systems, complementing the current support for Siemens, GE, and Philips. This will enable immediate deployment of the MRI pulse sequences developed in Aim 1 across both preclinical and clinical MRI scanners from all four major vendors.
3. We will conduct both animal and human MRI studies using various systems—including the 7T Bruker scanners at the University of Arizona (UofA) and Barrow Neurological Institute (BNI); the 3T Siemens Skyra at UofA; and the 3T GE and Philips scanners at BNI. We will evaluate the implemented pulse sequences based on image quality and consistency across data acquired at the same magnetic field strength (i.e., consistency across two 7T scanners; consistency across three 3T scanners).

Background and Significance:

Although numerous promising MRI pulse sequences for Alzheimer's research have been developed by various research groups, their widespread adoption remains limited due to a lack of vendor support and the time-intensive process required to implement these sequences across different MRI platforms. This challenge can be addressed using the open-source MRI pulse sequence language, Pulseq[1], which enables the implementation of pulse sequences across MRI scanners from GE, Siemens, Philips, and Bruker. Interpreters required to run Pulseq files are already fully developed and available for GE, Siemens, and Philips systems; however, the Bruker interpreter still requires updates to achieve full compatibility.

Our proposed study—which (1) implements advanced MRI pulse sequences with strong relevance to Alzheimer's research using the Pulseq language, (2) updates the Pulseq interpreter for the Bruker MRI system, and (3) evaluates the quality and consistency of these sequences across both preclinical

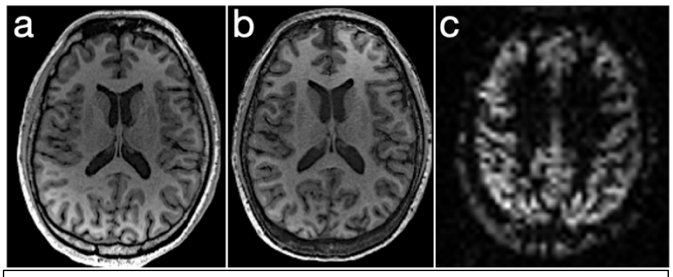


Fig 1: Pulseq-produced MRI data of a) T1-weighted MP-RAGE, b) T1-weighted segmented EPI, and c) cerebral blood flow map based on pCASL.

and clinical MRI scanners (Bruker, GE, Philips, Siemens)—is important for several key reasons. First, this work enables cross-comparison between animal and human imaging data using a unified set of multi-contrast MRI pulse sequences. While imaging parameters must be adjusted based on species and magnetic field strength, the ability to investigate the same physiological processes—such as blood-brain barrier integrity using diffusion-weighted pCASL—across species with comparable sequences is essential for effective translational research. Second, by using *Pulseq*-based implementations, MRI sequences and protocols can be standardized across different clinical MRI vendors (e.g., 3T GE, Siemens, and Philips), which is critical for enabling large-scale, multi-site Alzheimer's research with harmonized imaging data.

Preliminary Data:

Our lab has been developing a series of MRI pulse sequences using *Pulseq* language, supporting ongoing human MRI studies. For example, Fig 1 shows human MRI data obtained with our implemented Pulseq program for a) T1 MP-RAGE, b) T1-weigthed segmented EPI, and c) cerebral blood flow map based on pCASL.

Experimental Designs and Methods:

First, we will use *Pulseq* language to implement the following MRI pulse sequences.

a) pCASL with a 3D-bSSFP readout module and multiple post-labeling delay times: The proposed 3D-bSSFP based pCASL is expected to provide high-quality cerebral blood flow map free from geometric distortion and chemical-shift artifact, which typically reduce pCASL data obtained with EPI or GRASE readout modules. In addition, the implemented 3D-bSSFP pCASL sequence with multiple post-labeling delay will provide data with enhanced robustness (particularly in studies that include participants from different age groups; or with neurological conditions).
b) high-resolution and dynamic diffusion MRI (based on segmented EPI): The proposed dynamic diffusion MRI is capable of measuring pvCSF dynamics, which reflects glymphatic activity with great implication for Alzheimer's research.
c) diffusion-weighted pCASL: The diffusion-weighted pCASL sequence will be used to assess blood-brain barrier integrity without the need for contrast agent injection, which is important for human MRI research.

Second, our team member will update the existing *Pulseq* interpreter for our current Bruker ParaVision software version, so that *Pulseq* programs can be evaluated in animal studies using our 7T Bruker systems (in UofA and BNI). The *Pulseq* interpreters for GE, Siemens and Philips have already been updated to immediately support imaging studies in human MRI systems.

Third, we will conduct a series of animal and human imaging experiments to evaluate the performance of the implemented MRI pulse sequences across various systems—including the 7T Bruker scanners at UofA and BNI; the 3T Siemens Skyra at UofA; and the 3T GE and Philips scanners at BNI. Specifically, we will evaluate MRI data quality (in terms of signal-to-noise ratio, contrast-to-noise ratio, spatial resolvability, artifact level, spatial-temporal-resolution, test-retest reliability) for both animal and human MRI. In addition, we will evaluate the consistency across data acquired at the same magnetic field strength (i.e., consistency across two 7T scanners; consistency across three 3T scanners).

Proposed One-Year and Long-Term Outcomes:

One-year goal: Within one year, multiple advanced MRI pulse sequences critical for Alzheimer's research—including distortion-free pCASL for measuring cerebral blood flow, high-resolution dynamic diffusion MRI for assessing perivascular CSF and glymphatic activity, and diffusion-weighted pCASL for evaluating blood-brain barrier integrity—will be available across Bruker, Philips, GE, and Siemens platforms, enabling both translational and multi-site MRI studies. Long-term impact: The developed pulse sequences and the enhanced Pulseq framework—including

the updated Bruker interpreter—will provide a robust foundation for future translational and multi-center imaging research in Alzheimer's disease.

Year End Progress Summary:

During the 2025–2026 funding period, substantial progress was made toward the proposed goal of developing cross-vendor MRI pulse sequences for translational Alzheimer's disease research using the open-source Pulseq framework.

For Aim 1, we successfully continued the development and evaluation of several advanced MRI pulse sequences relevant to Alzheimer's disease research. Particular emphasis was placed on arterial spin labeling (ASL) MRI methods for measuring cerebral blood flow. Using the Pulseq framework, our team developed and evaluated a customized pseudo-continuous arterial spin labeling (pCASL) sequence with novel background suppression strategies designed to reduce chemical-shift artifacts while preserving perfusion sensitivity. Initial human imaging studies were successfully completed on the University of Arizona Siemens Cima.X MRI system. These studies demonstrated the feasibility of using Pulseq-based implementations to generate high-quality ASL data while providing additional flexibility for sequence development and optimization.

For Aim 2, progress was made toward improving cross-platform compatibility of Pulseq-based MRI pulse sequences. Development and testing efforts continued for deployment of Pulseq programs across multiple MRI vendors. The project further strengthened collaborations among investigators at the University of Arizona and Barrow Neurological Institute, creating a framework for future multi-site and multi-vendor evaluations of advanced MRI methods relevant to Alzheimer's disease research.

For Aim 3, pilot human imaging studies were conducted to evaluate image quality and technical performance of the implemented Pulseq sequences. These studies generated preliminary data supporting future cross-vendor validation efforts. While complete evaluation across all planned MRI platforms remains an ongoing effort, the current project successfully established the technical foundation necessary for subsequent implementation and harmonization studies.

The AAC-supported project also contributed directly to workforce development and trainee education. Undergraduate researcher Aidan Dolby played a major role in Pulseq sequence development, image reconstruction, and data analysis. This work resulted in the submission of abstracts to both the 2026 Arizona Alzheimer's Consortium Annual Meeting and the 2026 American Association of Physicists in Medicine (AAPM) Annual Meeting entitled "Background Suppression with Simultaneous Chemical Shift Artifact Reduction in Arterial Spin Labeling." These presentations disseminate project findings to both Alzheimer's disease researchers and the broader medical imaging community.

Several challenges were encountered during the project. Development of highly specialized MRI pulse sequences across multiple vendor platforms requires extensive software testing, sequence optimization, and hardware-specific modifications. In addition, implementation of advanced ASL methods required careful optimization of background suppression timing and image reconstruction methods to preserve perfusion sensitivity while reducing artifacts. Despite these challenges, the project achieved important technical milestones and generated preliminary data supporting future expansion.

Progress made during this funding period has positioned the project for continued growth. Building upon the results generated through this AAC award, we submitted a competitive AAC FY27 proposal entitled "Harmonized Cross-Vendor MRI Pulse Sequences for Assessing Blood–Brain Barrier Integrity in Diabetes and Alzheimer's Disease." In addition, the preliminary data and technical developments generated through this project are contributing to ongoing NIH grant activities focused on Alzheimer's disease, brain aging, glymphatic function, and advanced MRI technology development.

Overall, the project has advanced the development of harmonized MRI methodologies for Alzheimer's disease research, strengthened collaborations across Arizona institutions, provided meaningful trainee education opportunities, and established a foundation for future translational and multi-site neuroimaging studies

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Investigating the Impact of Transcranial Magnetic Stimulation (TMS) on Amyloid and Tau Clearance via Glymphatic Function in Prodromal Alzheimer's Disease. Ying-hui Chou, ScD, Nan-kuei Chen, PhD, Steven Rapcsak, MD, Nicholas Ashton, PhD. University of Arizona; Banner Alzheimer's Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

Alzheimer's disease (AD) is characterized by the accumulation of amyloid-beta (Aβ) plaques and tau neurofibrillary tangles, contributing to neuronal dysfunction and cognitive decline[1,2]. The glymphatic system, a brain-wide clearance pathway, plays a crucial role in removing these pathological proteins[3-5]. This project aims to investigate the potential of repetitive transcranial magnetic stimulation (rTMS) to enhance glymphatic function and subsequently reduce plasma Aβ and tau levels in individuals with prodromal AD. We will utilize advanced MRI techniques to assess glymphatic function; and plasma biomarkers to quantify Aβ and tau. This study will provide critical insights into the therapeutic potential of rTMS for promoting Aβ and tau clearance and potentially delaying AD progression.

- **Aim 1:** To determine the effect of rTMS on glymphatic function, as measured by diffusion tensor imaging along the perivascular space (DTI-ALPS) and dynamic diffusion-weighted imaging (dDWI), in individuals with prodromal AD.
- **Aim 2:** To evaluate the impact of rTMS on plasma levels of Aβ42/40, p-tau217, GFAP, and NfL in individuals with prodromal AD.
- **Aim 3:** To investigate the extent to which changes in glymphatic function mediate the relationship between rTMS condition (active vs. sham) and changes in plasma AD biomarkers.

Background and Significance:

Impaired glymphatic clearance is increasingly recognized as a key factor in AD pathogenesis[3-5]. Compelling evidence underscores the glymphatic system's critical role in the removal of Aβ and tau proteins from the brain[3,6-8]. This system facilitates the circulation and exchange of cerebrospinal fluid (CSF) and interstitial fluid (ISF) along cerebral vasculature, enabling the efficient clearance of metabolic byproducts, including Aβ, from brain interstitial spaces[3,9]. In healthy systems, Aβ, a normal neuronal byproduct, is effectively cleared via astrocyte-mediated glymphatic processes[10,11]. This clearance typically exhibits a diurnal rhythm, peaking during slow-wave sleep when enhanced neural synchrony optimizes fluid exchange within perivascular spaces[9,12,13]. Conversely, compromised glymphatic clearance within the central nervous system results in the accumulation of these neurotoxic proteins in neuronal tissue, exacerbating neurodegeneration and accelerating disease progression. Given its pivotal role in brain homeostasis, the glymphatic system presents a promising therapeutic target for AD prevention and treatment[4,14].

A critical question remains: how can we effectively modulate the glymphatic system? Preclinical evidence indicates that brain stimulation significantly improves glymphatic efficiency[15-20]. Repetitive transcranial magnetic stimulation (rTMS), a non-invasive neuromodulatory approach, has demonstrated efficacy in accelerating glymphatic activity, reducing cerebral Aβ burden, and enhancing cognitive function in AD mouse models (APP/PS1, 5xFAD)[16,17]. These benefits are associated with increased glymphatic clearance[16,17], potentially driven by rTMS-induced neuronal synchronization. Furthermore, stimulus-evoked neural rhythms have been shown to substantially augment glymphatic waste clearance in murine models[18,19].

Despite the promising findings from animal studies, there exists a gap in evidence regarding the effects of brain stimulation on the glymphatic system in humans. This lacuna underscores the

critical need for research that translates these neurophysiological insights into the human context to validate the potential therapeutic implications. This proposed study aims to address the critical gap in knowledge by directly investigating the relationship between rTMS, glymphatic function, and plasma Aβ and tau levels in individuals with prodromal AD. By elucidating these mechanisms, we can pave the way for developing novel rTMS-based therapies to potentially delay AD progression.

Preliminary Data:

For the past five years, our lab has specialized in stimulating the parieto-hippocampal network to enhance cognitive function in individuals with mild cognitive impairment (MCI) and cognitively normal (CN) adults. This approach employs diffusion MRI to precisely target a personalized superficial parietal region structurally connected to the hippocampus. In a reproducibility study (N = 30, age: 67.2 ± 7 years; females: 22), we demonstrated that diffusion-MRI-guided targeting exhibited significantly higher reproducibility than functional-MRI-guided methods[21]. Specifically, 60% of diffusion-MRI-guided targets remained stable across two MRI scans, compared to only 7% for fMRI-guided targets. Utilizing this diffusion-MRI-guided approach, we have shown that rTMS enhances associative memory and increases resting-state functional connectivity within the parieto-hippocampal network in MCI patients[22].

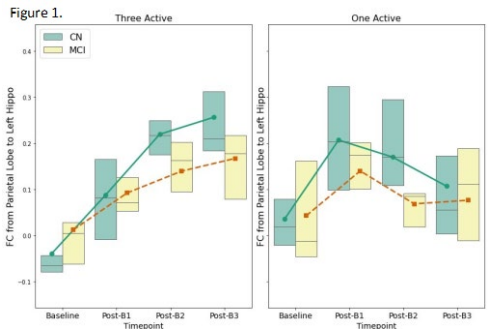


Figure 1.

To explore the optimal rTMS dosing strategy, we compared the effects of three active rTMS sessions (Three Active) versus a single active session followed by two sham sessions (One Active) on functional connectivity. Both rTMS conditions involved three sessions, separated by 60-minute intervals to maximize therapeutic benefit[23-25]. Twenty participants with MCI underwent both rTMS conditions in a crossover design. Our findings demonstrated a significant increase in parieto-hippocampal functional connectivity following the Three Active condition compared to the One Active condition ($p < .001$), suggesting a dose-dependent effect of rTMS (Figure 1). This finding strongly supports our proposal for three treatment sessions per day in this project.

Experimental Designs and Methods:

Participants. This study will recruit 30 individuals, aged 50 to 80, who meet the diagnostic criteria for mild cognitive impairment (MCI). Prior to enrollment, participants will be screened for MRI compatibility and the absence of TMS contraindications. Individuals with a history of seizures, significant neurological or psychiatric comorbidities (other than MCI), or current use of medications that could interfere with cognitive performance will be excluded.

Study Design. This study will employ a randomized, sham-controlled, cross-over design. Participants will be randomly assigned to one of two sequences: (1) Active rTMS followed by sham rTMS or (2) Sham rTMS followed by active rTMS. A washout period of 8 weeks will be implemented between the two rTMS condition to minimize potential carryover effects.

rTMS Intervention. The active stimulation condition will involve 3 daily intermittent theta burst stimulation (iTBS) sessions, a protocol selected for its demonstrated efficiency and effectiveness[26], administered with 60-minute inter-session intervals for 5 consecutive days. This interval strategy, informed by in vitro animal models[24,25], aims to maximize cumulative iTBS effects. iTBS will be applied to the superficial brain region exhibiting the highest structural connectivity with the left hippocampus, employing a methodology validated in our prior research[21,22]. This protocol is designed to induce long-term potentiation (LTP)-like plasticity within

the parieto-hippocampal network. During the sham stimulation condition, a sham coil will replicate the sensory aspects of active iTBS without delivering therapeutic magnetic stimulation.

Outcome Measures. Primary outcome measures, including cognitive performance, glymphatic function, and plasma biomarkers reflecting AD pathology, will be acquired at 4 discrete time points per participant: pre- and post-stimulation for each iTBS condition (i.e., active and sham). Cognitive performance will be evaluated using the NACC UDS 3.0 Neuropsychological Battery, assessing changes across key cognitive domains[27]. Glymphatic function, crucial for brain clearance, will be quantified using DTI-ALPS[28] and dDWI[29,30]. DTI-ALPS utilizes conventional diffusion tensor imaging to analyze water diffusion along perivascular spaces, inferring glymphatic flow efficiency by measuring the directionality of water movement. dDWI captures the dynamic movement of fluid within the brain over time by acquiring a series of diffusion-weighted images at different time points, providing insights into the rate of fluid exchange and overall glymphatic clearance. Plasma biomarkers—Aβ42/40, p-tau217, GFAP, and NfL—will be analyzed by Dr. Ashton's Biomarker Program. Additionally, sleep quality, a potential modulator of AD pathology and glymphatic function, will be assessed as a secondary outcome using the Pittsburgh Sleep Quality Index[31].

Statistical Analysis. Aim 1: To compare changes in DTI-ALPS and dDWI measures between active and sham iTBS conditions, we will employ a linear mixed-effects model. This model will include condition (active vs. sham) as a fixed effect and participant as a random effect, accounting for within-subject correlations. **Aim 2**: To assess differences in plasma Aβ42/40, p-tau217, GFAP, and NfL levels between active and sham iTBS conditions, linear mixed-effects models will be utilized. These models will include iTBS condition as a fixed effect and participant as a random effect, allowing for the analysis of repeated measures and individual variability. **Aim 3**: To examine whether changes in glymphatic function and sleep quality mediate the effect of iTBS condition (active vs. sham) on changes in plasma AD biomarkers, we will conduct mediation analyses using structural equation modeling or path analysis. We will assess the significance of indirect effects using bootstrapping methods. Statistical significance will be set at $p < 0.05$.

Proposed One-Year and Long-Term Outcomes:

This project will be the first study examining rTMS effects on glymphatic function and AD plasma biomarkers in prodromal AD. If successful, it will demonstrate the therapeutic potential of rTMS in enhancing glymphatic clearance and improving cognitive outcomes in individuals at risk for AD. Additionally, this one-year pilot project will yield critical preliminary data, which will serve as a robust foundation for future NIH R01 grant applications in 2026, enabling us to design and execute larger, more comprehensive clinical trials. Specifically, the data will inform power calculations, refine our understanding of the iTBS mechanism, and strengthen the rationale for long-term studies investigating the potential of iTBS to modify AD pathology and improve cognitive outcomes.

Year End Progress Summary:

We examined changes in the diffusion tensor imaging analysis along the perivascular space (DTI-ALPS) index following theta-burst stimulation (TBS) in 36 older adults with mild cognitive impairment (MCI). DTI-ALPS is an MRI-based measure that reflects the efficiency of the brain's glymphatic waste removal system, as it quantifies how easily water molecules move along the perivascular spaces where waste is cleared. Participants underwent sessions of active TBS and sham TBS, with DTI-ALPS measurements acquired before and after each condition. Our sham-controlled findings reveal the capacity for TBS interventions to modulate glymphatic function and highlight a significant APOE ε4 effect. Specifically, ε4 carriers exhibited a lower baseline DTI-ALPS index ($p < 0.05$, Cohen's d = 0.610), suggesting reduced glymphatic function, which was selectively responsive to TBS interventions ($p < 0.005$, Cohen's d = 1.71). Further, within this subgroup, TBS-induced increases in glymphatic function correlated with memory improvements ($r = 0.42$-0.46, $p < .05$). These results provide novel evidence that TBS can

modulate glymphatic function in humans and raise interesting questions about the relevance of APOE status. Further research is needed to elucidate the mechanisms underlying these effects and their therapeutic implications.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Determining the impact of Alzheimer's disease on the capacity of acetylcholine to reorganize hippocampal neural ensembles in response to novelty and motion. Stephen Cowen, PhD, Carol A. Barnes, PhD, Asier Aristieta PhD. University of Arizona; Arizona Alzheimer's Consortium.
**NOTE: postdoc Asier Aristieta moved to UCSD shortly after support began, and his responsibilities were taken over by postdoc Matthew Schmitt.*

Specific Aims:

- Specific Aim 1: Acetylcholine release in the hippocampus is involved in the storage of novel episodes and spatial navigation. Using fiber photometry and Neuropixels ensemble recordings, we will determine if sub-second acetylcholine release induced by exposure to novel spatial environments results in lasting changes in neuron-neuron interactions and whether these interactions are diminished in TgF344-AD rats.
- Specific Aim 2: Theta- and gamma-band oscillations in the hippocampus organize neural ensemble activity related to navigation and memory formation. These oscillations are strongly regulated by acetylcholine and motion (*e.g.*, speed, acceleration). We hypothesize that relationships between motion and neural ensemble and local-field activity are reduced in Alzheimer's disease. This will be assessed by measuring sub-second hippocampal acetylcholine release and neural ensemble activity in freely-behaving TgF344-AD rats performing a novel string-pulling task and running on tracks

Background and Significance:

The hippocampus receives significant cholinergic input from neurons in the medial septum, and medial septum neurons and acetylcholine (Ach) release in the hippocampus are involved in memory, REM sleep, and navigation. Furthermore, cholinergic receptors in the hippocampus are reduced in AD. Altered cholinergic signaling may contribute to episodic and spatial memory deficits observed in early to mid-stage AD. Ach release is notably dynamic, with medial septum cholinergic neurons being active during exploration, novelty, and REM sleep. With the recent emergence of fiber photometry, it has become clear that localized Ach concentrations change with sub-second precision. Pulsatile release of Ach may be timed to neural oscillations and the occurrence of significant events and actions. Indeed, our preliminary data indicates that acetylcholine release in the striatum pulsates at a 2-Hz rhythm in freely behaving animals (Figure 1). Similar patterns of release likely occur in the hippocampus and may regulate the transition between memory retrieval and memory encoding.

Preliminary Data, Experimental Design and Methods:

What follows is a bulleted summary of preliminary data demonstrating feasibility:

- Over the last year, my laboratory has refined and advanced our capacity to collect and analyze real-time release of neuromodulators (dopamine and acetylcholine) using fiber photometry. We have acquired data from >15 freely behaving animals using the GRAB-DA3 (dopamine) and 1 recording using a GRAB-Ach (acetylcholine) sensor.
- In the summers of 2023 and 2024, Dr. Cowen and his graduate students acquired simultaneous photometry and Neuropixels measurements from freely behaving mice while teaching a hands-on course at Woods Hole, MA. This demonstrates our capacity to integrate Neuropixels and fiber photometry measurements. (Aim 1,2)
- My laboratory has acquired neural ensemble data using Neuropixels 2.0 probes (n = 14 rats). These probes have 5,000 recording sites and offer next-generation measurement of

neural activity. Data was collected from the hippocampus and thalamus as animals performed track running, the novel string-pulling behavior described In Aim 2, and surrounding ketamine injection. To investigate between neuron interactions, we have applied analyses described in our manuscript in Brain (Vishwanath et al. 2024). We also identified strong theta-phase alignment to the paw 'pull' during the string-pulling behavior.

- My lab maintains a colony of TgF344-AD rats (2-12 mo.). We collaborate and share this resource with Dr. Barnes (AAC proposal), Dr. Bartlett (AAC proposal; Surgery), and are submitting a AAC grant with Dr. Elizabeth Hutchinson (AAC proposal) – BME.

Proposed One-Year and Long-Term Outcomes:

Timeline: Mo. 1-3) Inject rats with rAAV-hSyn-ACh3.0 and implant fiber photometry probes. Wait 3 weeks for expression and verification of Ach signal. Implant Neuropixels probes. Train rats to run the circular track and perform the string-pulling task. Mo. 4-6) record Ach and ensemble activity (Aim 1,2). Mo. 7-10) Analyze neural and behavioral data and histology Mo. 11-12) Make figures and finalize analyses for planned grant submissions.

Grant Submission: Results will be used for NIA R01 grant applications. A R01 (NIA PAR-22-093) and a R03 (NIA PAR-23-179). The general hypothesis addressed is that AD disrupts Ach release and associated neuron-neuron interactions in response to novel context and motion.

Year End Progress Summary:

Through AAC support, we purchased the rAAV-hSyn-ACh3.0 GRAB-Ach sensor, performed surgeries and injected 10 rats with the virus, and implanted optical fibers in these animals for measuring Ach release. Ach recordings were acquired from a total of 7 rats during the period of support. This represented a major advance for our laboratory given that we had only acquired data from one animal using this sensor previously. Further, these measurements provided considerably preliminary data for NIH grant submissions (Fall 2026) and many troubleshooting opportunities.

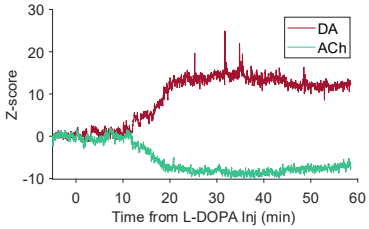


Figure 1. Concentration of acetylcholine and dopamine change in opposing directions following L-DOPA injection. We speculate that suppression of Ach release is due to the activation of dopamine D2Rs known to be present on Ach presynaptic terminals.

We also discovered that combining the Ach sensor (GRAB-Ach) with a dopamine (GRAB-DA2h) sensor allowed simultaneous measurement of both neuromodulators and provided valuable information about their interactions. Few studies to date directly compare inter-modulator dynamics during behavior. To accomplish this, we injected both sensors in a subset of rats and measured changes in concentration following L-DOPA (a dopamine precursor) injection. Under these conditions, DA and Ach concentrations moved in opposing directions (See Figure 1). We speculate that this was due to the activation of inhibitory dopamine D2 receptors as these receptors are present on Ach presynaptic terminals. These results are now key preliminary data for grants that will explore the interplay between neuromodulators and how such interplay is affected by aging and Alzheimer's disease.

Obstacles: While electrical artifacts are not a concern with fiber photometry (unlike electrophysiology), we encountered large, unexpected, and intermittent artifacts in the recorded data typically in the form of large, unexpected level-shifts in the data. After investigation, we determined that these artifacts were created by micromovements of the fiber at the junction between the tether and the rat's head as well as from the coiling of the optical fiber. To address this, we purchased a 'screw top' connector that more firmly affixed the fiber to the animal, stiffened

the cable, and added strain relief to the tether. Given the troubleshooting and artifacts in the Ach measurements initially, we decided that it was too risky to attempt a dual Neuropixels + fiber photometry probe given the cost of the Neuropixels probe (>$2300/probe). Now that most of the artifact and uncertainties surrounding photometric recordings have been resolved, we plan on performing dual recording in the next 6 months.

A second obstacle was the TgF344-AD rat model. As we learned over the year and from reading some recent published reports, these animals are minimally motivated by food reinforcement and are generally unwilling to run on mazes or pull strings (the originally planned task for the AAC grant). Consequently, we developed a novel task where animals performed a nose poke to stop a moving treadmill. This worked well as while the TgF344-AD model was not motivated to work for food, they were motivated to stop working (by stopping the treadmill via a nosepoke). We then adjusted this task to examine the animal's capacity to time intervals of 5, 10, and 12 seconds as the hippocampus appears to play an important role in the representation of the passage of time (and is interval representation is impaired in AD). The results of this novel behavior will be presented at this year's AAC and SFN conferences and are near ready for publication. We have also begun measuring neural activity using Neuropixels probes (ventral hippocampus) in these rats. Unfortunately, we have not yet measured Ach in these animals as they perform this new task but that is a major goal for the fall. **Thus, a key outcome from AAC support was the development of a novel behavior tailored to the study of time-interval estimation and neurophysiological recording in these AD model animals.**

Planned grant submissions: As stated in the original proposal we will apply for an R03 (NIA PA-25-246 (formerly NIA PAR-23-179) in the fall on the topic of dual measurement (dopamine + Ach). And an R01 (formerly NIA PAR-22-093) focused on Neuropixels ensemble recording combined with GRAB-Ach measurement in our TgF344-AD animals to determine how Ach release is affected.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Targeting Neuroinflammation in Alzheimer's Disease: LXA4-Specific FPR2 Assay Development. Kevin Gaffney, PhD. University of Arizona Center for Innovation in Brain Science; Arizona Alzheimer's Consortium.

Specific Aims:

The overarching goal of this proposal is to identify in vitro assays for the optimization of LXA_4-mimicking small molecule FPR2 agonists focusing on direct FPR2 engagement and neuroinflammation-relevant phenotypic assays. A hallmark anti-inflammatory effect of LXA_4 is to induce FPR2 homo-dimerization while also decreasing FPR2/FPR1 hetero-dimerization whereas pro-inflammatory ligands have the opposite effect on dimerization. Consequently, in *Specific Aim 1*, we will leverage our previous FPR2 NanoBiT experience to develop: (i) an FPR2 homo-dimerization NanoBiT assay; (ii) an FPR2-FPR1 hetero-dimerization NanoBiT assay. We will then compare the dimerization effects of anti-inflammatory LXA_4 to pro-inflammatory W peptide in both dimerization systems.

Several studies have documented the direct *in vitro* effects of lipoxins on microglia. In the BV2 mouse microglia cell line, treatment with LXA_4 and 15-epi-LXA_4 has been shown to decrease LPS-induced IL-1β and TNF-α expression and NF-κB signaling. While BV2 microglia are a well-studied model, in our hands, commercially available BV2 cells are inconsistently responsive LPS likely due to high, unreported passage numbers. As a result, *Specific Aim 2*, we will optimize assay conditions for assessing the anti-inflammatory effects of LXA_4 in LPS-treated immortalized microglial (IMG) cell line, a newly reported, commercially available microglia cell line.

Background and Significance:

Neuroinflammation is an early and central feature of Alzheimer's disease (AD), arising alongside amyloid pathology, cognitive impairment, and metabolic dysfunction, and may reflect a failure of normal inflammation-resolution biology. In healthy tissue, inflammation transitions from pro-inflammatory lipid signaling toward specialized pro-resolving mediators (SPMs), including lipoxins, resolvins, maresins, and protectins, which promote microglial phagocytosis, suppress inflammatory cytokines, and increase IL-10. Aging and AD disrupt this balance, with elevated pro-inflammatory LTB_4 and reduced pro-resolving LXA_4 in the brain, hippocampus, and CSF, including correlations between lower CSF LXA_4 and worse cognitive performance. Consistent with this biology, LXA_4 and 15-epi-LXA_4 improve cognition and reduce Aβ, p-tau, inflammatory cytokines, NF-κB activation, and microglial reactivity in multiple AD mouse models, but their therapeutic development is limited by instability and synthetic challenges. This proposal therefore hypothesizes that metabolically stable small molecules that mimic LXA_4 signaling through FPR2 could reduce neuroinflammation and slow, halt, or reverse cognitive decline in AD, and seeks to develop FPR1/FPR2 NanoBiT dimerization assays that distinguish pro- versus anti-inflammatory FPR2 agonists while optimizing IMG microglial assays to support discovery of LXA_4-like small-molecule FPR2 agonists for AD.

Preliminary Data, Experimental Design and Methods:

We have previously shown that we can: (i) successfully transfect HEK293 cells with FPR2; (ii) successfully measure agonist-induced protein-protein interactions between FPR2 and β-arrestin via NanoBiT assay. This sets the stage for the extension of this FPR2-based NanoBiT protein-protein interaction assessment of FPR2 dimerization.

Proposed One-Year and Long-Term Outcomes:

Data and findings from this proposed project will be submitted for presentation at relevant scientific conferences and in peer-reviewed manuscripts. Importantly, this work takes the crucial steps necessary to identify in vitro FPR2 target engagement and anti-neuroinflammation phenotypic assays. These assays will set the stage for carrying out high throughput screening for LXA_4-mimicking small molecule FPR2 agonists and provide the preliminary data necessary to pursue NIH and/or DoD funding and industry and investor support.

Year End Progress Summary:

We successfully completed Specific Aim 1 by developing and optimizing two complementary NanoBiT dimerization assays: an FPR2 homodimerization assay and an FPR1-FPR2 heterodimerization assay. We first established the FPR2 homodimerization system using complementary C-terminal SmBiT- and LgBiT-tagged FPR2 constructs. Assay optimization began with plasmid titration studies comparing baseline and agonist-induced luminescence under DMSO control conditions and following treatment with the FPR2 agonists FPR43 and W peptide at 10, 100, and 1,000 nM. We subsequently evaluated whether N-terminal signal sequences improved assay performance by comparing constructs tagged with HA or prolactin. These optimization studies identified a final assay configuration of 200 ng FPR2-SmBiT and 200 ng FPR2-LgBiT, each bearing an N-terminal prolactin signal sequence.

Using this optimized FPR2 homodimerization assay, we generated concentration-response profiles for a panel of FPR2 ligands, including FPR43, W peptide, ACT- 389949, BMS-986235, LXA4, and BML-111. All tested compounds robustly induced FPR2 homodimerization, as evidenced by increased NanoBiT luminescence. This dimerization response was reduced by pre-treatment with the FPR2 antagonist WRW4.

We then applied the same optimization workflow to establish an FPR1-FPR2 heterodimerization NanoBiT assay. Across both the homodimerization and heterodimerization systems, we observed that both pro-inflammatory and pro-resolving FPR2 ligands induced receptor dimerization. This finding differs from prior literature suggesting that pro-resolving ligands selectively increase FPR2 homodimerization while decreasing FPR1-FPR2 heterodimerization, with pro-inflammatory ligands producing the opposite pattern. In our assay systems, dimerization appeared to be a general property of FPR2 agonist engagement rather than a ligand-class-specific differentiator.

For Specific Aim 2, we optimized an IMG microglial cell assay to assess suppression of LPS-induced inflammatory signaling. Drawing on our prior experience with LPS-induced TNF-α time-course studies other myeloid cells, we selected a 16-hour LPS exposure as a practical endpoint that provides robust inflammatory induction while remaining compatible with routine assay execution. We evaluated a range of LPS concentrations in IMG cells (5, 10, 25, and 50 ng/mL) and found that 10 ng/mL LPS provided the most useful assay window. This condition induced TNF-α while avoiding an excessively strong inflammatory response that could limit the ability of active compounds to suppress the LPS-driven signal. Using this optimized assay, we confirmed pharmacologic responsiveness with two positive controls. Dexamethasone significantly reduced LPS-induced TNF-α, validating the assay as a general anti-inflammatory readout. In parallel, the FPR2 agonist FPR43 also significantly reduced LPS-induced TNF-α relative to DMSO-treated controls, supporting the utility of IMG cells for evaluating FPR2-linked anti-inflammatory activity.
Together, the completion of Specific Aims 1 and 2 established the core in vitro assays needed to support optimization of pro-resolving, LXA4-mimicking small-molecule FPR2 agonists, including direct receptor engagement assays and a neuroinflammation-relevant microglial phenotypic assay. **Due to these efforts, we were able to apply for an $11.6 million grant for this program to the NIH.**

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Advancing Cognitive Health Disparities in Mexican-origin Adults with MASLD. David O. Garcia, PhD, FACSM, Adriana Maldonado, PhD, Matthew Huentelman, PhD, Nan-Kuei Chen, PhD, Susan Aguiñaga, PhD, Nicholas Ashton, PhD; Shannon Lindemer, MS. University of Arizona; Translational Genomics Research Institute; University of Illinois Urbana-Champaign; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

Specific Aim 1: Conduct qualitative research to assess knowledge, attitudes, and beliefs about cognitive impairment in Mexican-origin adults with and without metabolic-dysfunction associated steatotic liver disease (MASLD).

We will recruit 20 Mexican-origin adults in Southern Arizona and conduct semi-structured interviews to explore understanding of cognitive health, perceived risk factors, barriers to completing cognitive health assessments, barriers and facilitators to healthcare access, and strategies for communicating cognitive health risks.

Specific Aim 2: Examine the link between MASLD and cognitive impairment using a combination of neuropsychological tests and MRI in 40 Mexican-origin adults.

We will recruit 40 Mexican-origin adults in Southern Arizona to assess cognitive function using neuropsychological tests of executive function, working memory, and episodic memory, in combination with structural neuroimaging via MRI. FibroScan® will be used to quantify liver steatosis and fibrosis. Hypothesis: MASLD status will be associated with lower cognitive function scores and greater structural brain changes, particularly in memory and executive function regions such as the hippocampus and prefrontal cortex.

Exploratory Aim: Evaluate the feasibility, usability, and acceptability of remote blood collection for Alzheimer's disease blood-based biomarkers using Capitainer® dried plasma spot technology and pTau217 analyses in collaboration with Dr. Nicholas Ashton and Banner Sun Health Research Institute (BSHRI).

Background and Significance:

Mexican-origin adults experience disproportionately high rates of metabolic dysfunction-associated steatotic liver disease (MASLD), cardiometabolic disease, mild cognitive impairment (MCI), and Alzheimer's disease (AD), yet remain underrepresented in cognitive aging, biomarker, and neuroimaging research. MASLD affects approximately 43% of Mexican-origin adults and is closely linked to obesity, type 2 diabetes, hypertension, and dyslipidemia. Emerging evidence suggests MASLD may contribute to cognitive decline through inflammatory, vascular, and neurodegenerative pathways and is associated with poorer cognitive performance and structural brain changes. This pilot study examined relationships among liver health, cognitive function, and structural brain changes while exploring community perceptions of cognitive health and barriers to assessment among Mexican-origin adults in Southern Arizona. An exploratory aim evaluated the use of Capitainer® dried plasma spot technology and take-home blood collection kits for remote pTau217 biomarker collection to improve access to Alzheimer's disease screening and research participation in underserved communities.

Preliminary Data, Experimental Design and Methods:

The project leveraged the Nosotros Comprometidos a Su Salud existing community-engaged recruitment pool. Since January 2022, the team has screened more than 6,000 Mexican-origin adults in Southern Arizona, approximately 60% of whom had MASLD and agreed to be re-contacted for future studies. This established community partnership supports the feasibility of

recruiting Mexican-origin adults for cognitive testing, liver assessment, biospecimen collection, and MRI.
Specific Aim 1: Twenty Mexican-origin adults, with and without MASLD, completed FibroScan®, MoCA-S, and semi-structured interviews conducted in Spanish. Interviews explored cognitive health beliefs, perceived risk factors, barriers and facilitators to cognitive assessment and healthcare access, and preferred approaches for communicating cognitive health information. Interviews were recorded, transcribed, translated as needed, de-identified, and will be analyzed using thematic analysis in NVivo using established qualitative rigor procedures. **Aim 2:** Forty Mexican-origin adults, with and without MASLD, completed a FibroScan®, anthropometric measurements, questionnaires, neuropsychological testing, blood collection, and a structural MRI. Cognitive domains assessed included global cognition, executive function, working memory, and episodic memory using the UDS v2 – Spanish battery. MRI was performed on a 3T Siemens MAGNETOM Cima.X scanner to evaluate hippocampal and cortical regions implicated in cognitive decline, as well as white matter hyperintensities. Planned analyses include descriptive statistics, group comparisons by MASLD status, and regression models adjusted for age, sex, and education. **Aim 3:** Participants completed three Capitainer® dried plasma spot collections: (1) staff-assisted baseline collection, (2) at-home self-collection using a take-home kit, and (3) staff-assisted collection during the MRI visit. Outcomes included adherence, usability, sample quality, acceptability, and successful generation of pTau217 measurements. This provides preliminary data regarding the feasibility of remote blood-based biomarker collection in community-based research settings.

Proposed One-Year and Long-Term Outcomes:
One-Year Outcomes: We successfully recruited and enrolled the target sample of Mexican-origin adults; completed all study procedures, including a FibroScan®, neuropsychological testing, structural MRI, blood biomarker collection, buccal swab collection, and qualitative interviews; evaluated the feasibility, usability, and acceptability of remote pTau217 collection using Capitainer® dried plasma spot technology; and preparing to complete preliminary data analyses to disseminate findings through conference presentations, abstracts, and manuscript development.

Long-Term Outcomes: Findings from this study will: support future NIH and foundation-funded research focused on cognitive health disparities, blood-based biomarkers, and neuroimaging among Hispanic populations; the development of scalable, community-based approaches for implementing blood-based biomarker collection and Alzheimer's disease research in underserved settings; improving access to early Alzheimer's disease screening and detection among Mexican-origin and other Hispanic populations; and inform culturally responsive interventions and dissemination strategies aimed at reducing MASLD-related cognitive health disparities and Alzheimer's disease risk.

Year End Progress Summary:
During the 2025–2026 reporting period, substantial progress was made toward all project objectives. Recruitment, community engagement, neuropsychological testing, MRI procedures, and biomarker collection were successfully implemented for all study aims. In addition, the Nosotros team was successful in strengthening collaborations among the University of Arizona, Translational Genomics Research Institute (TGen), Banner Sun Health Research Institute (BSHRI), and the Arizona Alzheimer’s Consortium. Community engagement efforts continued through partnerships with Nosotros and the TGen Mobile Health Unit, increasing research access among underrepresented Hispanic populations. Qualitative interviews provided valuable information regarding perceptions of cognitive health, Alzheimer’s disease, cognitive testing, MRI

participation, and barriers to care among Mexican-origin adults. We also completed structural MRI procedures and extensive neuropsychological testing using culturally and linguistically appropriate measures for Spanish speaking Mexican-origin adults. A major accomplishment during this funding period was the implementation of the pTau217 feasibility study (exploratory aim), in collaboration with Dr. Nicolas Ashton and BSHRI, which evaluated the real-world feasibility and acceptability remote biomarker collection. Preliminary observations indicate high participant engagement and successful completion of collection procedures across all time points.

A few challenges were encountered during the study. Two participants were unable to complete MRI procedures due to claustrophobia or other MRI-related concerns, requiring additional recruitment efforts. The study also experienced loss to follow-up of two participants between visit 1 and visit 2. Further, while some participants reported being comfortable completing study procedures in Spanish during initial screening, they later experienced some difficulty understanding neuropsychological testing instructions during in-person visits, highlighting the importance of considering language proficiency, literacy, and cultural factors when conducting cognitive assessments in diverse populations. The Capitainer® dried plasma spot feasibility study presented challenges, as some participants were concerned about performing at-home blood collection incorrectly and required more instruction and support than anticipated. Despite these challenges, participant engagement remained high, and the lessons learned will help improve future community-based biomarker and cognitive health research efforts.

Data cleaning and analysis are currently underway. Findings from this study will support future abstracts, conference presentations, manuscript development, and larger grant applications focused on blood-based biomarkers, neuroimaging, cardiovascular health, and Alzheimer's disease prevention among Hispanic populations. Particular emphasis will be placed on evaluating the potential of remote blood collection technologies to increase access to Alzheimer's disease biomarker testing in rural and underserved Mexican-origin communities

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Examining autobiographical memory integration in older adults: social functions and neural dynamics. Matthew Grilli, PhD, Sarah Hennessy, PhD, Jessica R. Andrews-Hanna, PhD.
Department of Psychology, University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

1. **Investigate how autobiographical memory integration facilitates social and communication functioning in older adults. H1:** Autobiographical memories that are more integrated in both *time* and *meaning* will be rated as easier to understand and more informative, interesting, authentic, and relatable.
2. **Assess the neural dynamics supporting temporal autobiographical memory integration in younger and cognitively healthy older adults. H2:** Distinct neural states will be observed corresponding to varying autobiographical timescales during recall. Transitional probabilities between states will be higher in healthy older compared to younger adults, reflecting greater neural flexibility related to navigating autobiographical memories across time.

Background and Significance:

Individuals with AD demonstrate a fragmented sense of time and difficulties with narrative sequencing, suggesting overall challenges with contextualizing memory across varying timescales (time integration). Additionally, individuals with AD cognitive impairment often experience alterations in sense of self, which may be exacerbated by the reductions in the ability to recall self-defining memories (meaning integration). Conversely, episodes of lucidity in AD can include temporary improvement in time orientation and clarity of self. Thus, autobiographical integration is a key concept to study in AD. However, to understand the functions of integration and the mechanisms underlying their decline in AD, we must first investigate healthy older adults, a population in which these skills may instead be enhanced.

This project is significant as it will: 1) establish whether age-related shifts in autobiographical memory recall style (i.e., memories with additional temporal and meaning context) confer social and communication *benefits* and 2) be the first to investigate how these shifts are supported by whole-brain network dynamics, using modern neuroimaging and machine-learning methods. Pilot data will elucidate the functions and mechanisms related to age-related changes in autobiographical memory recall, which will ground future research in AD.

Preliminary Data, Experimental Design and Methods:

In preliminary analyses, we investigated whether cognitively healthy older adults have a more stable self-concept, which may be supported by shifting autobiographical recall style and more time to integrate memories into their sense of self. We observed that older adults have greater *self-representation stability*, particularly at the highest levels of the data distribution, indicating more congruent self-appraisals across time. Stability was additionally positively related to well-being, particularly in older adults. Self-representation stability is likely linked to autobiographical memory integration, where memories that are temporally contextualized within one's life story and contain self-related meaning bidirectionally support stability. Preliminary fMRI analyses of a different dataset involving passive rest and a "think aloud" stream of consciousness period suggest that healthy older adults' brain networks are more integrated than young adults.

We propose two related studies to assess our aims. In **Study 1 (Aim 1)**, we will recruit a nationally representative sample of 200 adults aged 18-99 through an online research platform (*Prolific Co.*).

Participants will read autobiographical memories and provide subjective ratings for 1) interest, 2) authenticity, 3) information learned about the storyteller, 4) relatability, and 5) understandability by indicating agreement to statements (i.e., "I found this story to be interesting"). Memories will be generated to vary on 1) Time Integration and 2) Meaning Integration (Integrative vs. Non-Integrative) while keeping topic, length, and valence consistent. Five matched sets of memories will be generated, and each participant will be randomized to a set. We will test **H1** with a 4x2 ANOVA, with Time and Meaning Integration predicting each of the rated outcome variables.

In **Study 2 (Aim 2)**, we will recruit 12 participants (6 younger adults and 6 cognitively healthy older adults) to participate in a pilot fMRI study examining the neural dynamics of temporal autobiographical memory integration. The fMRI task will include two conditions: 1) A free-recall autobiographical memory task ("please describe, out loud, a memory of your past"). Researchers will later annotate the audio recordings, marking moments when participants naturally shifted between timescales; 2) A guided-recall autobiographical memory task, in which participants will describe events focusing on integration. Hidden Markov models will be trained on the fMRI data from each task to identify latent brain states corresponding to autobiographical timescales. Specifically, we will assess whether these states align with researcher-annotated and cued transitions for the recall tasks. To test **H2,** transitional probabilities between brain states will be calculated to quantify the flexibility of timescale-related neural state shifts. These probabilities will be compared between groups to assess age-related differences in the neural dynamics supporting temporal integration of autobiographical memory.

Proposed One-Year and Long-Term Outcomes:

One-year outcomes: This pilot study will result in: 1) essential behavioral data to justify the relevance of studying time and meaning integration in investigations of social and communication in older adults with and without AD, 2) critical pilot neuroimaging data that may be used to strengthen this year's grant applications, including renewal of current NIA R01 funding (MPIs: Grilli & Andrews-Hanna).

Long-term outcomes: This project will yield multiple collaborative publications on autobiographical memory processes and functions in healthy aging. This pilot work will serve as the foundation to ground grant proposals related to AD. Specifically, we aim to use these pilot data to build an R01 proposal investigating behavioral and neural indices of autobiographical memory integration in individuals with AD, aimed at early detection via aberrant integration patterns. Memory integration difficulties may not only be an early marker of AD but may also represent a potential therapeutic target for mitigating social challenges and disruptions in one's sense of self, both of which contribute to loneliness and behavioral and psychological symptoms of dementia in early-stage AD. Dr. Hennessy additionally intends to leverage these pilot data for an F32 training grant to support her future related work on AD at the University of Arizona.

Year End Progress Summary:

1. For Aim 1, we collected a representative sample of 300 older adults who participated in an online study (via Prolific) assessing the impact of meaning and time integration on the degree to which memories were perceived as interesting, informative, clear, relatable, authentic, and vivid. Findings indicate that memories higher in meaning and/or time integration are significantly more interesting, informative, clear, relatable, authentic, and vivid, even when matched for essential memory features (topic, valence, word count, episodic specificity), suggesting that integration plays an important role in the social and communicative functions of autobiographical memory. This provides essential behavior data to justify the relevance of studying integration of autobiographical memories in older adults with and without AD. We have drafted a manuscript reporting these data, which will be submitted for publication this summer.

2. For Aim 2, we have collected fMRI data from 12 pilot subjects. Preliminary analyses of pilot data show that, while participants are engaging with autobiographical integration (both time and meaning), BOLD activity is higher in the DMPFC and midline core subsystems of the Default Mode Network, including the temporal pole, precuneus, posterior cingulate, and the dorsomedial prefrontal cortex. We will continue to analyze these data with the intention of supporting this year's grant applications (including renewal of current NIA R01 funding (MPIs: Grilli & Andrews-Hanna), for other future applications to the NIA, and for postdoctoral training grants for Dr. Sarah Hennessy.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Advanced dMRI applications to detect microscale pathology and glymphatic-lymphatic pathophysiology in the TgF344-AD rat model. Elizabeth Hutchinson, PhD, Carol Barnes, PhD, Stephen Cowen, PhD, Mitchell Bartlett, PhD. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

Promising diffusion MRI (dMRI) techniques for microstructure and cerebrospinal fluid (CSF) fluid dynamics have been developed at UA and demonstrated in normal rat brain imaging. We will apply these promising approaches to detect pathology and glymphatic-lymphatic disruption in the TgF344-AD rat strain according to two aims:

1) Specific Aim 1: Identification of microstructural abnormalities in the TgF344-AD rat brain by mean apparent propagator (MAP) MRI. In the past decade, newer and more sophisticated dMRI technologies such as mean apparent propagator MRI (MAP-MRI)(*1, 2*) have emerged that are promising for the detection of specific pathologic cellular alterations(*3*) even in the context of complex brain disorders such as AD. However, these newer dMRI frameworks have not been successfully migrated toward use in patient populations. ***Goal #1: To identify and validate MAP-MRI markers of AD pathology in the F344TG-AD rat model.***
2) Specific Aim 2: 2D cortical slice mapping of water velocity to measure CSF transport disruptions in the TgF344-AD rat cortex. There is a particular need to better determine the role of glymphatic-lymphatic waste clearance dysfunction in the natural course of pathogenesis that accompanies AD. Novel dMRI-based methods could provide non-contrast measurement of fluid dynamics associated with CSF transport. ***Goal #2: To apply a novel 2D cortical slice mapping of CSF speed to detect glymphatic-lymphatic abnormalities in the F344TG-AD rat model.***

Background and Significance:

The F344TG-AD rat model recapitulates key features of human Alzheimer's Disease (AD) pathology. AD pathology is notoriously difficult to study in pre-clinical rodent models as transgenic mice do not naturally express the same protein isoforms as humans and it is necessary to use humanized transgenic lines with reduced pathologic complexity – i.e. without frank neurodegeneration, with only beta-amyloid (Aβ) or Tau pathology, but not both – and may not sufficiently recapitulate dysfunction of the glymphatic-lymphatic system. Transgenic rats can provide an important alternative to mice and the TgF344-AD rat line(*4*) in which amyloid precursor protein and presenilin-1 mutations are introduced has emerged as a leading pre-clinical model because the brains of these rats demonstrate hippocampal Aβ plaques followed by the spontaneous emergence of neurofibrillary tangles (NFTs) and neurodegeneration that recapitulates the complete set of human AD pathology. Additionally, these rats demonstrate inflammation(*5*), vascular pathology(*6, 7*) and memory-related behavioral deficits(*4, 8, 9*). We have selected this model for the study of complex pathophysiology that mimics human AD and may exhibit glymphatic-lymphatic dysfunction.

The promise of novel microstructural markers of AD Pathology with dMRI**.** The identification of sensitive and specific brain imaging markers is a primary goal for diagnostic neuroimaging in AD to more accurately detect pathology in the early stages and differentiate AD from other disorders and comorbidities. Advanced dMRI approaches are highly promising to develop new markers as they can uniquely probe the microscale tissue environment to report and differentiate cellular and microscale pathology. While conventional dMRI – especially diffusion tensor imaging (DTI) – has been incorporated in AD research for decades, the impact has been limited and currently DTI is not used for clinical diagnosis as it cannot specifically identify AD

pathology. MAP-MRI makes use of the non-Gaussian dMRI signal collected at strong diffusion weighting and in doing so provides improved specificity for mapping microscale anisotropy and water restriction. The resulting metric maps probe microscale information not accessible with DTI.

Detection of glymphatic-lymphatic pathophysiology. The recent discovery and description of cerebrospinal fluid (CSF) mediated waste clearance via the glymphatic-lymphatic(*10-13*) system has cast new light on the pathophysiology of numerous neurologic disorders especially those with major components of protein aggregation and accumulation, most notably AD(*14-16*). While the spatiotemporal patterns of hallmark AD pathologies – NFTs and Aβ plaque formation – are well-characterized and even define post-mortem diagnosis in humans(*17*), the relationship of other pathologic cellular and physiologic changes that accompany or precede these proteinopathies are not well understood. If CSF can be measure non-invasively and directly (i.e. without the injection of dye or contrast agent) the promise of novel and translationally relevant markers of glymphatic-lymphatic health is improved. Such techniques have been demonstrated in phantoms(*18, 19*) and our current work has migrated these to the in vivo rat brain(*20*).

Preliminary Data, Experimental Design and Methods:

The MRI technologies proposed in this work have been developed and demonstrated by the Hutchinson lab in the translational bioimaging resource (TBIR) using the 7T Bruker BioSpec MRI system. MRI processing, mapping and analysis tools have also been optimized. The Tg344-AD rat model is an uncommon and powerful resource that the Barnes and Cowen labs have established at the UA and begun to study over a range of neuroscience-based projects. A colony Tg344-AD rats is currently maintained and behavioral, electrophysiology and mechanistic studies are ongoing in their labs. The proposed MRI experiments will complement ongoing work across all PI labs, enrich the foundation for observations in this model and support future funding proposals.

Proposed One-Year and Long-Term Outcomes:

- The data collected during this project period can support 1-2 student abstracts for submission to a national conference (e.g. SfN, BMES or ISMRM) and may be sufficient for the preparation and submission of a research paper depending on quality of results.
- We expect that this work will fill gaps noted in the summary statement of a previously submitted but unsuccessful NIH R21 proposal on related projects. The PIs of this project will assess the best course to apply for national funding as results emerge and at the end of the project period. The scope of proposal (e.g. R21 or R01) will depend on the results of the proposed work and parallel research studies in the respective PI labs. A CDMRP or NIH mechanism with AD focus will be a likely target.
- Long term outcomes will be to leverage the Tg344-AD model and novel dMRI approaches in a larger body of research funding and productivity across our labs and to make these methods available to collaborators. If non-invasive markers specific to early AD pathologic changes and CSF transport disruption can be established, then new scientific questions can be asked and interventions tested.

Year End Progress Summary:

Overview. The progress made during the project period of this proposal accomplished all goals related to the collection of MRI data and additional data sets were also collected from fixed male brains by reorganization of student funding to cover scanning costs as one student (Carlson) joined an ADRD-related T32 during the project period. A total of 11 female rats with were imaged both in vivo and their brains ex vivo as well as six male rats with ex vivo scanning only. Approximately 50/50% of each sex was from the WT/TgF344AD lines and the MRI included all scanning proposed. The in vivo data has been processed and the diffusion MRI maps generated

as proposed, although initial analyses of results are waiting on direct confirmation of genotype group following immunohistochemistry (IHC).
All brain IHC has been planned and the reagents and antibodies have been purchased during the project period. Meningeal lymphatic vessel (MLV) staining is planned and all chemicals purchased as well.

Challenges Encountered. There was a delay in project progress of several months due to major MRI scanner issues and 2-3 months of downtime as well as image quality issues severe enough to require re-collection of some data. Dr. Hutchinson contributed to an ***MPI S10 proposal to replace the faulty parts*** and currently, the MRI scanner is operational, but the in vivo MRI scans for half of the rats were delayed and ex vivo MRI scans all required re-collection (ongoing). Since ex vivo MRI acquisition precedes IHC, this also resulted in a delay for the IHC parts of the proposal. Fortunately, ***FY27 AAC funding was awarded to Dr. Cowen*** that will enable the completion and extension of this scientific goal.

Findings. The main findings of the proposal were methodologic in nature and included confirmation of phase contrast velocity (pcv) mapping in this rat line. The MRI technique is novel and will be presented in an ***abstract by Rhea Carlson at the AAC Fall Conference***. Additionally, Dr. Hutchinson has submitted an ***R01 that will advance rigor of interpretation for the dMRI-flow methods*** used in this project.
We expect to describe microstructural findings related to aim 1 once the genotypes are confirmed by IHC. Since this should be completed by the end of the 2026 Summer, we are targeting a ***"late breaking" abstract submission to the SfN conference for Rhea Carlson*** and she will use T32 travel funding to attend and present this work in the Fall of 2026.

Long-term Outcomes. In addition to the abstracts and grants that were submitted are or directly expected (in bold/italics above), we expect that the project progress of this period is foundational to future grants, manuscripts and publications in the next period and future years. Both aims have critical and novel aspects for long-term planning. The microstructural sensitivity of advanced dMRI (Aim 1) has strong promise, but cannot be effective without rigorous validation. The combination of the collected dMRI data from the present project period with the next stage of experiments in the nexy period (Cowen, FY27) will provide critical insight into the value of advanced dMRI markers of AD relevant pathology in this rat model by careful comparisons between behvioral outcomes, MRI and IHC. We did not plan a manuscript publication for the present project period, but it would be reasonable to begin planning for this in the next period. Similarly, the results generated can be used by any or the PIs to support dMRI markers of AD pathology in any future grant proposals. The development and application of slow-flow velocity mapping using single encoded dMRI (Aim2) is novel and potentially impactful. Depending on the ultimate findings of this study and the comparison with MLV staining, there will be sufficient outcomes to report as part of a methodologic manuscript or as a stand-alone paper. Additionally, the images and results generated could be used by any of the PIs in proposals on a range sof topics from methods development to application to AD outcomes in the TgF344AD model.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Using Noninvasive Electrical Brain Stimulation to Improve Language in the Logopenic variant of Alzheimer's Disease. Aneta Kielar, PhD, CO-Is: Katlyn Nickels, PhD, SLP, Pelagie Beeson, PhD, CCC-SLP, Steven Rapcsak, MD. Speech Language and Hearing Sciences, Cognitive Science GIDP, BIO5 Institute, University of Arizona; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Specific Aims:

Specific Aim 1 is to evaluate the therapeutic value of combining phonological treatment with fMRI-guided anodal transcranial direct current stimulation (tDCS) on language performance in individuals with Alzheimer's neuropathology, logopenic Primary Progressive Aphasia (lvPPA). Anodal tDCS will be applied to individually determined location within the preserved frontal regions responsible for phonological processing.

Specific Aim 2 is to examine changes in neural function in response to treatment with active tDCS versus sham stimulation using measures of brain activation and functional connectivity.

Specific Aim 3 is to examine the mediating role of Brain-Derived Neurotrophic Factor (BDNF) genotype and blood serum neurotrophin levels on response to language therapy combined with tDCS. If anodal tDCS influences functional connectivity by enhancing synaptic plasticity, which relies on activity-dependent BDNF secretion, we expect that individuals with the typical val/val genotype will exhibit increased connectivity in the language network. These changes should correspond with elevated serum BDNF levels and behavioral improvements. This is a multi-level exploration of PPA pathology across molecular, brain networks and behavioral indicators. We will comprehensively examine the relationship of treatment responses with neuroimaging and blood biomarkers.

Background and Significance:

In lvPPA, cortical atrophy associated with Alzheimer's pathology results in a language profile characterized by reduced and slowed speech production, word retrieval difficulties, and impaired reading and writing. Effective pharmacological treatments for lvPPA are currently unavailable, and research in the field of treatment is still in its nascent stages. Given the progressive nature of lvPPA, **there is an urgent need to develop interventions that can remediate language impairment and identify factors that enhance treatment response.** Encouragingly, our research group has shown promising outcomes demonstrating that language training can improve or slow the loss of language abilities by leveraging not yet damaged components of the language network and the relatively preserved memory system**.** In this proposal, we aim to advance this line of research by exploring the potential value of pairing evidence-based language treatment with neuromodulation effects using noninvasive transcranial direct current stimulation (tDCS). We implement multiple neurobiological indicators to optimize tDCS effects for each participant by determining electrode placement using individual structural and functional MRI scans and modeling electrical current flow to target preserved language regions for a given individual. **The aim is to maximize treatment effects in a relatively short period of time**. We hypothesize that intervention with language therapy paired with tDCS, will engage of residual components of the language network and reverse or slow language decline. Prior research suggests that the neuroplastic changes induced by tDCS may be linked to the activity-dependent release of BDNF. The relationship between response to tDCS intervention, BDNF genotype, and blood serum levels of neurotrophins has not been previously investigated in lvPPA. Thus, we anticipate important new knowledge from our unique multi-level examination of relations among the BDNF gene, BDNF blood serum concentration, AD plasma biomarkers and alterations in brain functional connectivity linked to treatment responsiveness in active tDCS compared to sham.

Preliminary Data, Experimental Design and Methods:
Our data indicates a large advantage for active tDCS treatment for assembling phonemes into words (tDCS pre = 45% vs. post = 70%, effect size = 0.93; sham pre = 62% vs. post = 67%, effect size = 0.13), a skill that supports reading and writing. The generalization gains were significantly larger after treatment with active tDCS (pre = 61% vs. post = 81%, effect size = 0.87, $F(1, 41) = 16.06$, $p < 0.001$), but were not significant after treatment with sham stimulation (pre = 79% vs. post = 87%, effect size = 0.43, $F(1, 41) = 1.59$, $p = 0.215$). Overall, there was greater treatment gain and generalization for active tDCS combined with phonological intervention than for phonological intervention with sham.

Experimental Designs and Methods: **Participants** will be individuals diagnosed with lvPPA (~40-80 years old), randomized to receive active tDCS+language treatment or sham+language treatment in a cross-over design. **Phonological treatment paired with tDCS** was initiated in the week following pre-treatment assessments, baseline neuroimaging scans and current flow modelling and will be implemented over two sequential 2-week phases (with five 60-min sessions/week = 10h of treatment for each phase) separated by a 2-month rest interval with no treatment. Two months after completion of the second treatment phase, follow-up testing will be administered. The participant, therapist, tDCS technician and those involved in data collection and analysis will be blinded to tDCS condition. **Computational Modeling:** To determine the precise electrode position and optimal current flow at the target location, we modelled tDCS current flow using SIMNIBS v4.0.1 using each participant's structural MRI. **Pre-post tDCS assessments.** To assess direct treatment effects, generalization and maintenance, participants completed multiple baseline probes and a series of cognitive-linguistic assessments before and after each phase of intervention and at 2-months follow-up **(Aim 1). Functional MRI scans** were acquired in resting state and during language tasks to localize brain activation that will *guide optimal electrode positioning during tDCS intervention.* Individual changes in neural function and network connectivity in response to treatment were examined with task and resting-state fMRI at each follow-up time point. White matter connectivity was determined by multi-shell diffusion weighted imaging (DWI) **(Aim 2). For BDNF genotyping (Aim 3),** buccal swabs were collected from all participants. The rs6265 SNP genotyping is currently performed at Arizona Molecular Clinical Core. Levels of neurotropic protein in the blood serum will be measured from peripheral blood samples collected at baseline, at each post-treatment assessment point and at 2-months follow-up. The statistical models will examine the individual behavioral and neural responses to the intervention relative to the clinical variables and BDNF genotype and blood serum levels of neurotrophins.

Proposed One-Year and Long-Term Outcomes:
Our preliminary work demonstrates that we are well positioned to immediately recruit new participants and initiate assessments and treatment. Data analyses will be finalized in early 2026 and manuscripts will be submitted for publication throughout 2025 and 2026. **Feasibility.** Our team is fully capable of implementing the proposed research, and we have access to the necessary instrumentation and technical support. We have demonstrated consistent patient safety, comfort, and satisfaction. **Future directions**. The results obtained will support our plan to obtain R01 funding (~$3.5 million) through the NIH-NIA PAR-22-093: Research on Current Topics in Alzheimer's Disease and Its Related Dementias. Submission deadlines are scheduled for October 2026 and January 2027. The new grant pre-application has been submitted to the *FY26 AZRP Transforming Care Award Funding Opportunity: HT942526AZRPTrCA* Congressionally Directed Medical Research Program (CDMRP), The Defense Health Agency.

Year End Progress Summary:

During the award period from 07/01/25 to 06/30/26, we screened and enrolled participants, increasing the sample size to n = 18 individuals who completed the full trial of the intervention. Retention has been high, and the placebo-controlled trial continue until early 2026. We are in contact with the aphasia/neurology clinics in the Tucson community and in the UA Speech, Language and Hearing Clinic. We give presentations to the community to communicate our study and findings. To accomplish Aim 3, in the first quarter of the grant, we developed protocols for the collection of biomarker samples (buccal swabs and blood draws). This process required protocol specific personnel training and new Human Subjects Protection approvals. The biomarker collection resulted in active collaboration with the UA Clinical and Translational Research Center, with Arizona Molecular Clinical Core for analysis of the samples and with UA Health Science Biorepository for preprocessing and storage of the biological samples.
The collection of samples is completed and analyses are ongoing.

The case data from this study has been published in *Frontiers in Human Neuroscience* and the group results with n=12 (6 TDCS-first and 6 sham-first) and group results have been published in the *Journal of Speech Language and Hearing Research.* Our results indicate that individuals with lvPPA showed significant improvement in phonological transcoding skills in response to behavioral intervention, but those who received active tDCS first showed stronger gains in phonological manipulation ability and generalization to written language, which contained more grammatical sentences with increased meaningful content and more accurate spelling. These data provide compelling evidence supporting our individualized intervention approach that targets phonological deficits in logopenic PPA with brain stimulation. Specifically, we found that improved phonological skills resulted in better text-level writing ability relevant to everyday life.

The treatment results have been presented at the 63rd annual Meeting of the Academy of Aphasia, SanDiego, USA. We organized a symposium presentation for the 63rd Annual meeting of the Academy of Aphasia that took place in October 2025. The data from this project have been presented at the Arizona Alzheimer's Consortium 26th Annual Scientific Conference in September 2025, Clinical Aphasiology Conference, Albuquerque, New Mexico, USA in May 2025, and 17th Annual Meeting of the Society for Neurobiology for Language, Gallaudet University, Washington DC, USA in September 2025. The analysis of fMRI data is ongoing.

ARIZONA ALZHEIMER'S CONSORTIUM
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Retinal Neurovascular Signaling in Alzheimer's Disease. Paulo W. Pires, PhD and Erika Eggers, PhD. Department of Physiology, University of Arizona College of Medicine; Arizona Alzheimer's Consortium.

Specific Aims:

The specific aim of this project is to determine if the function and morphology of the retina and its vasculature are impaired in a model of AD. We will measure retinal neuronal and vasculature structure and function through cell labeling, electroretinograms (ERG), and vascular reactivity measurements. Given previous reports suggesting retinal ganglion cell functional changes[1-3], we expect loss of ganglion cells in *5x-FAD* mice due to Amyloid-β (Aβ) accumulation. We also expect that we will observe vascular degeneration and inflammatory activation of glia and microglia. Further, we expect reductions in the sensitivity and light adaptation of ERG waves, which will spatially correlate with A*β* accumulation. We expect that pathological Aβ will reduce retinal ERG and vascular dynamic responses, including stimulus-induced, in a dose-dependent manner.

Background and Significance:

The *5x-FAD* show significant retinal and visual deficits. This includes a loss of visual acuity at 45 days of age[1], reduced Visual Evoked Potentials at 2 months of age[1], reduced retinal function measured by *in vivo* electroretinograms (ERG) by 3 months[4] and dysfunctional ganglion cells[5] by 2-3 months[2]. Aβ accumulation is found in the retina as early as 1 month of age[1] and changes in glutamate and GABA distributions are shown by 2 months of age[2]. This is an early functional phenotype, as significant cognitive impairment is not shown until 6 months of age[1], suggesting that the retina is affected early in the disease. Little is currently known about the retinal vasculature in AD models. A previous study showed structural vascular changes in male *5x-FAD* mice[6], but did not investigate dynamic microvascular regulation. Further, nothing is currently known about retinal neurovascular regulation and vasculature in females (which account for ~70% of AD cases). Our proposal will fill this critical *knowledge gap*.

In summary, we plan to investigate retinal AD damage in the *5x-FAD* model that is ideal to study pathological processes of AD at early and late stages without the influence of aging. It is crucial to understand how AD damages the retina, as this is an early site for AD nervous system damage and could be used for clinical screening[7,8]. This proposed collaboration would make use of the strengths of both the Eggers and Pires laboratories (retinal physiology and pathology and microvascular function / structure, respectively) to delineate the retina as a valuable mechanistic example and as a screening tool for diagnostics and experimental therapeutics. We will gain knowledge on the specific retinal cells that are damaged and how this affects retinal neuronal and vascular physiology, leading to a significant step forward in the field.

Preliminary Data, Experimental Design and Methods:

Specific Aim: Determine if the function and morphology of the retina and its vasculature are impaired in a model of AD. Retinal neuronal and vascular damage have been shown in mouse models of AD[7,9], including in *5x-FAD* mice[1,2,4,5]. However, it is also unclear which specific neurons are dysfunctional or how the vasculature is affected in the AD retina. We propose to fill these knowledge gaps using *5x-FAD* (6-9 months old) mice.

Sub-aim 1: to assess loss of specific retinal neuron types[10,11], changes in vascular density / structure and glial activation using immunohistochemistry. The Eggers lab has considerable experience in using immunohistochemistry in whole-mount retinas to label specific retinal cell types and receptors[10-12]. Eyes will be removed, retinas dissected out whole, fixed and labeled with immunohistochemistry for neuronal nuclei (DAPI), rod and cone photoreceptors (PNA), rod

bipolar cells (PKCα), amacrine cells that release GABA/glycine/dopamine (GAD65/67, GlyT1, TH) and ganglion cells (RBPMS). Vascular density and tortuosity will be assessed using immunofluorescence in whole-retina mounts by labeling retinal vasculature endothelial cells (Isolectin-B/CD31) and smooth muscle cells (smooth muscle myosin heavy chain) and the components of the neurovascular unit will be analyzed by labeling pericytes (PDGFR-β + NG2), microglia (Iba1/ P2X12), astrocytes (GFAP), and Müller glia (Glutamate synthase) in WT and 5x-FAD mice. We will determine if the number, shape, and interactions of these retinal vascular, glial, and microglial components are different between WT and *5x-FAD* retinas and will perform a detailed analysis of cell morphology (branching, length of branches, size of soma), as recently described by the Pires laboratory[13].

Sub-aim 2: measure retinal function using *in vitro* ERG, as previously described by the Eggers lab[14]. To determine how retinal activity is changed in the *5x-FAD* model, we will use our *in vitro* ERG system to measure summed retinal responses, which have been used in the Eggers laboratory to show retinal functional changes in early diabetes[14,15]. We will record the dark-adapted and light-adapted ERG in response to multiple intensities of light to determine if there are changes in the magnitude or timing of the *a* (photoreceptor), *b* (ON bipolar cell) and oscillatory potentials (inner retina) waves between control and AD retinas.

Sub-aim 3: quantify microvascular function using *ex vivo* pressure myography, as described by the Pires lab for cerebral arterioles[16]. In particular, we will assess whether: 1) acute Aβ exposure impairs the ability of isolated retinal arterioles from C57bl/6J mice to appropriately respond to changes in intraluminal pressure, also known as auto-regulation, increasing risk for vascular rupture and hemorrhages; 2) acute Aβ exposure impairs the ability of isolated retinal arterioles from C57bl/6J mice to dilate in response to physiological signals (metabolic – ADP and adenosine – and neuronal-derived – dopamine), leading to an imbalance in tissue energy expenditure and nutrient supply, resulting in retinal ischemic events; 3) auto-regulation and dilation are impaired in the retinal microvasculature of *5x-FAD*.

Sub-aim 4: assess retinal capillary integrity as a measurement of the blood-retina-barrier. This will be achieved by measuring vascular extravasation and accumulation of fluorescently-labeled dextran (3, 10 and 30 kDa) injected intravenously, as previously described by the Pires lab[13]. In addition, we will perform immunofluorescence labeling of protein important for maintenance of the blood-retina-barrier, particularly tight junction proteins (claudin-5, zonula occludens-1).

Proposed One-Year and Long-Term Outcomes:

One-Year Outcomes: We will determine if retinal neuronal and neurovascular unit structure and function are damaged in *5x-FAD*. Congruent with previous reports suggesting retinal ganglion cell functional changes[1-3], we expect loss of ganglion cells in *5x-FAD* due to Aβ accumulation. We also expect that, in *5x-FAD*, we will observe capillary degeneration, loss of retinal pericytes and activation of glia and microglia towards a pro-inflammatory phenotype. Further, we expect reductions in the sensitivity and light adaptation of ERG b-waves, which will spatially correlate with A*β* accumulation. We expect that pathological A*β* will reduce retinal ERG and vasoregulatory responses. Lastly, we expect that retinal microvascular responses will be impaired in the retinal of 5x-FAD, accompanied by an increase in leakiness of the blood-retina-barrier.

Year End Progress Summary:

To investigate the neurovascular unit in *5x-FAD* retinas we retinas from 9-month-old *5x-FAD*, labelled them for immunohistochemistry and imaged the retina with a confocal microscope. For each animal one eye was labeled for Astrocytes (GFAP antibody), pericytes (NG2 antibody), blood vessel endothelial cells (Isolectin B stain) and DAPI (nuclei stain). The other eye was labeled for ganglion cells (RBPMS antibody), β-amyloid (antibody), dopaminergic amacrine cells (tyrosine hydroxylase – TH antibody), and TOPRO (nuclei stain). The coverage and number of these cells was analyzed using ImageJ and statistics were calculated using Prism. Initial

comparisons were made to previous staining from the Eggers laboratory of 7-month-old C57Bl6J mice. Subsequently we also obtained 9-month-old C57bl/6J mice as controls for the *5x-FAD* mice and they were labeled in the same way.

So far we have found several changes in the *5x-FAD* mice that suggest disruption of the neurovascular unit. We found that a smaller percentage of the retinal area was covered by astrocytes and that astrocytes covered a smaller proportion of the blood vessels in the GCL. This was present even though the gross blood vessel area did not change. We also found that there was a reduction in the number of astrocyte somas associated with blood vessels and changes in the morphology of astrocyte endings. All of this suggest changes in the astrocytes to compensate for stress or neurovascular degeneration. We also found that there was a reduced area of capillaries in the GCL, INL and ONL in the *5x-FAD* retinas. Along with this there was an increased area covered by pericytes and % of capillaries covered by pericytes in the GCL. We also found no loss of dopaminergic amacrine cells. We are still in the process of measuring pericyte number, ganglion cell number and staining with β-amyloid. We are also working on repeating these measures to compare with the 9-month-old controls to ensure any of the changes we are seeing are not due to retinal aging. Given that 7-9 months old is still a relatively young mouse this seems unlikely based on the time course of retinal aging.

In addition, we are currently working on the isolation and cannulation of retinal arterioles. A major challenge this year has been to obtain mice to perform these experiments due to breeding issues (the *5x-FAD* colony in the Pires lab underwent a period without new litters). Another challenge was technical in nature, as one of the myography setups needed to perform these experiments was damaged, and just recently fixed. Even though the award period is ending, we will continue working on this project as we plan to collect preliminary for a MPI R01 in early 2027.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Development of Alzheimer's Disease-Focused Mitophagy Assays. Kathleen Rodgers, PhD.
University of Arizona Center for Innovation in Brain Science; Arizona Alzheimer's Consortium.

Specific Aim(s):

Mitophagy is the primary mechanism by which cells maintain mitochondrial quality. Recent data highlight the central role of mitochondrial dysfunction and impaired mitophagy in driving neuroinflammation and neurodegeneration in Alzheimer's disease (AD). As a result, therapies that stimulate mitophagy hold great potential to restore mitochondrial health and slow, or even reverse, neurodegeneration and cognitive decline in AD patients. Consequently, the primary goal of this proposal is to develop AD-relevant mitophagy assays to enable high-throughput screening of mitophagy inducers and accelerate the identification of potential therapeutic candidates.

Specific Aim 1: Development of a Neuron-Based Mitophagy Assay: In neurons, over-expression of human Tau has been shown to suppress mitophagy.[1,2] Therefore, in Specific Aim 1, we will develop a neuron-specific mitophagy assay in neurons over-expressing human Tau to mimic AD pathology.

Specific Aim 2: Development of a Microglia-Based Mitophagy Assay: In microglia, pro-inflammatory signals have been shown to suppress mitophagy and, conversely, stimulation of mitophagy reduces microglial release of pro-inflammatory release indicating a strong link between mitophagy and neuroinflammation.[3] Therefore, in Specific Aim 2, we will develop a microglia-specific mitophagy assay in LPS-treated microglia to mimic neuroinflammation in AD.

Background and Significance:

Mitochondria are dynamic organelles that generate the majority of cellular ATP via oxidative phosphorylation (OXPHOS) and coordinate diverse cellular processes including programmed cell death, calcium flux, and fatty acid metabolism. Mitochondria contain their own extranuclear genome. Relative to nuclear DNA, mitochondrial DNA (mtDNA) is uniquely susceptible to damage due to mtDNA's proximity to high energy oxygen radicals of OXPHOS, high frequency of replication, and limited repertoire of DNA repair machinery.[4] Mutations in mtDNA accumulate with age which contribute to mitochondrial dysfunction – such as reduced ATP production, altered mitochondrial dynamics, and elevated reactive oxygen species (ROS) production – and, in turn, reduce cellular/organ health and lead to chronic inflammation.[4] Due to the importance of mitochondria, cells have evolved a specialized autophagic process to turn over mitochondria called mitophagy. Mitophagy enables mitochondrial quality control by selectively removing damaged mitochondria. This process prevents the accumulation of dysfunctional mitochondria and sustains the bioenergetic fitness of a cell in response to stress.[4]

Impaired mitophagy is a key feature of Alzheimer's disease (AD), particularly in the hippocampus, where studies show a significant decline in mitochondrial degradation.[5,6] As a result, damaged mitochondria accumulate, increasing oxidative stress and driving neurodegeneration. This dysfunction is linked to changes in critical mitophagy regulators, including PINK1, Parkin, LC3-II, and p62, which show altered expression in AD, suggesting mitophagy failure at multiple levels.[5,7,8,9,10] Several AD-associated proteins directly contribute to these mitophagy deficits including Tau. Tau disrupts mitophagy by interfering with Parkin recruitment to damaged mitochondria in primary neurons and neuronal cell models.[1,2,5] Further, in microglia, pro-inflammatory signals have been shown to suppress mitophagy and, conversely, stimulation of mitophagy reduces microglial release of pro-inflammatory release indicating a strong link between mitophagy and neuroinflammation.[3] Mitophagy impairment in neurons and microglia may independently and synergistically exacerbate AD pathology through a pathological feedback loop between these two cell types.

Given the central role of mitophagy dysfunction in both neuronal and microglial pathology, we hypothesize that mitophagy inducers hold great potential to reduce neuronal loss and neuroinflammation and slow, or even reverse, cognitive decline in AD patients. To test this hypothesis, this proposal aims to take the first crucial steps by: (i) developing a neuron-specific mitophagy assay in neurons over-expressing human Tau to mimic AD pathology; (ii) developing a microglia-specific mitophagy assay in LPS-treated microglia to mimic neuroinflammation in AD. The successful development of these assays will provide a robust platform for screening and identifying small-molecule mitophagy inducers as potential treatments for AD.

Preliminary Data, Experimental Designs and Methods:

We have extensive experience in *in vitro* assay development including work with neurons, microglia, flow cytometry, viral transduction, and antibiotic selection, providing a strong foundation for developing the neuronal mitophagy assays outlined in this proposal.

Neuro-2a (N2a) mouse neuroblastoma cell line (CCL-131) and media were purchased from ATTC. Reporter plasmids were purchased from Addgene. These plasmids were cloned into lentiviral vectors and packaged at GenScript. N2a were transduced with lentivirus and then undergo selection to make a stable N2a cell line.

Proposed One-Year and Long-Term Outcomes:

Data and findings from this proposed project will be submitted for presentation at relevant scientific conferences and in peer-reviewed manuscripts. Importantly, this work takes the crucial steps necessary to develop neuron and microglia targeting mitophagy assays. These assays will set the stage for carrying out high throughput screen for mitophagy inducers in both of the cell types and provide the preliminary data necessary to pursue NIH and/or DoD funding.

Year End Progress Summary:

The development of an in vitro model to study Alzheimer's disease (AD) involved overexpressing the Tau protein and evaluating its effects on mitochondrial function and cell viability. The first step involved transient overexpression of the Tau protein. Neuronal cells (SH-SY5Y and H4 cells) were transfected with 0.1 µg of the plasmid for 72h and 48 h, respectively. High-resolution respirometry analysis showed no significant impact of Tau overexpression on mitochondrial function at either time point. Additionally, no reduction in cell number was observed.

Next, two higher plasmid concentrations (0.5, and 1 µg) were compared to the previous 0.1 µg in SH-SY5Y cells. Cells were transfected for 48 h and 72 h. In contrast to the previous results, respirometry analysis demonstrated reduced mitochondrial function in cells expressing 0.5 and 1 µg of plasmid at both time points, while 1 µg of plasmid nearly abolished mitochondrial respiration. A decrease in cell number was also observed across all tested concentrations. To confirm that the plasmid transfections were effectively expressing protein, SH-SY5Y cells were transfected with 0.5 µg of a plasmid encoding a FLAG-tagged protein. After 48 h of transfection, cells were stained for mitochondria, the FLAG tag, and nuclei using immunocytochemistry (ICC). Imaging revealed weak and highly variable protein staining among cells, suggesting inconsistent protein expression following plasmid transfection.

To overcome the inconsistent expression seen with transient transfections, we attempted develop constitutively expressing cell line using lentiviral transduction. SH-SY5Y cells were transduced with multiple lentiviral multiplicities of infection (MOIs), and successfully transduced cells were recovered using an antibiotic selection marker. However, a pronounced decline in cell viability was observed several days after selection. To determine whether the observed toxicity resulted from the selection marker itself, a selection-marker titration was performed. Cell death persisted even at low selection-marker concentrations, suggesting that constitutive Tau expression, rather than antibiotic toxicity, was responsible for the reduced viability.

Finally, a transduction system that minimized cellular toxicity was optimized. In addition to SH-SY5Y cells, N2a cells were transduced with a lentiviral Tet-On system, in which protein expression is induced by doxycycline in stably transduced cells. While SH-SY5Y cells exhibited significant toxicity following transduction and selection, N2a cells responded favorably and were successfully maintained after selection. Doxycycline concentration and induction duration were subsequently optimized using 0.1, 0.5, 1, and 2 μg/mL doxycycline in N2a cells treated for 2 or 3 days. Mitochondrial function and mitochondrial reactive oxygen species (ROS) production were assessed by respirometry and ROS measurements, respectively. No mitochondrial dysfunction or increase in ROS production was observed under the tested conditions, and no significant effect on cell viability was detected.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

The impact of *APOE* E4 on episodic and autobiographical memory: Episodic and semantic memory generation across the adult lifespan. Lee Ryan, PhD, Matthew Grilli, PhD, Matthew Huentelman, PhD, Stephanie Matijevic, PhD. University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

1. To determine whether episodic and semantic detail generation have separate trajectories across the adult lifespan. Specifically, we expect semantic detail to steadily increase with age, until plateauing in late mid-life. In contrast, we predict that episodic detail will be stable across young adulthood and early mid-life, until beginning to decline in later mid-life.

2. To test whether adults carrying at least one APOE E4 allele are distinct from non-carriers in their trajectories of episodic and semantic detail generation across the lifespan. We expect that APOE E4 carriers will produce fewer episodic details than non-carriers across the lifespan. We will also determine whether these differences are specific to autobiographical memory, or whether they mirror an episodic associative memory task, verbal paired associate learning.

Background and Significance:

When asked to describe autobiographical events, older adults will typically provide fewer episodic details and greater semantic details than younger adults (Levine et al., 2002; Gaesser et al., 2011; St Jacques, & Levine, 2007; Simpson, Eskandaripour, & Levine, 2023). The increase in semantic detail generation has been proposed to serve as a form of compensation for age-related reductions in episodic memory retrieval. However, recent work from our group casts doubts on the idea that age-related increases in semantic detail are compensatory. In a sample of younger adults (ages 20-41), we found that semantic detail generation increased steadily with age among younger to middle-aged adults, while episodic detail remained stable (Matijevic, Hoscheidt and Ryan, in press). In another sample of late middle-aged to older adults (ages 52-81), we observed linear episodic detail decreases with age, with no changes to semantic detail (Matijevic et al., 2022). Based on this work, we have proposed that there are separate trajectories for semantic detail and episodic detail generation across the adult lifespan. Specifically, we theorized that semantic detail increases throughout early adulthood until plateauing in late mid-life, while episodic detail begins its downward trajectory in late mid-life. Different mechanisms may drive the alterations to episodic and semantic detail generation across the lifespan. While semantic detail increases may be tied to the increasing complexity of semantic knowledge and changes to narrative approach with age, episodic detail reductions may be linked to age-related deficits in processes involved in episodic retrieval.

Furthermore, Grilli et al. (2018) found that older adult carriers of the APOE E4 allele provided fewer episodic details than age-matched non-carriers during an autobiographical memory assessment, with no difference in semantic detail generation nor on a variety of standard neuropsychological tests. Palmer, Huentelman and Ryan (2023) have proposed that the impact of APOE E4 on brain function may result in a cognitive phenotype, independent of Alzheimer's disease pathology, that is characterized in part by underutilization of episodic details. This cognitive phenotype may be specific to autobiographical memory, or it may impact all forms of episodic learning and memory. If the latter is correct, the decrease in autobiographical episodic detail should be apparent on other hippocampally-mediate memory tests, such as verbal paired associates learning. Studying both autobiographical memory and a novel learning and memory

task will help clarify whether the effects of APOE E4 on memory are specific to autobiographical memory or more general.

To date, most of the research on autobiographical memory has been conducted through comparisons of younger and older adults. Thus, we have little insight into autobiographical memory recollection in middle-age, and a poor understanding of how alterations to semantic and episodic detail generation unfold across the lifespan. We plan to fill this gap in the existing literature by conducting a study of semantic and episodic detail generation during autobiographical memory narration across the adult lifespan (ages 20-79). Utilizing MindCrowd, we aim to recruit participants from across the country to take part in recorded interviews conducted over Zoom, in which we will ask participants to recollect and describe autobiographical event memories. From this data, we will be able to characterize the trajectories of episodic and semantic detail generation across the adult lifespan. Because the participants are recruited through MindCrowd, we will be able to consider the relationship between patterns of autobiographical memory retrieval and retrieval on a hippocampally-mediate learning and memory task.

Preliminary Data:

This is an extension of the project that we began last year with funding from AAC. We have made good progress on the project with promising preliminary data. Data has been collected for more than half of the planned sample, and we are on track to complete data collection by June 30th. Blood samples are currently being processed in order to determine APOE E4 status. Preliminary data suggests that semantic details increase at younger ages, while older adults provide fewer episodic details than younger adults. However, we are currently underpowered to determine whether the APOE E4 allele impacts the adult trajectory for autobiographical memory and associative memory performance. We propose to double the number of participants in each age group in the coming year and to add associative memory performance measures (already available for the cohort) to our analyses.

Experimental Design and Methods:

We will expand the current cohort from 20 to 40 participants from each age decade between the ages of 20 and 79 (i.e. 20-29, 30-39, etc.) for a total of 240 participants. Participants will be recruited through MindCrowd, and thus have already completed a verbal paired associate memory task. Through Zoom interviews, participants update their medical history, and then describe 4 autobiographical event memories from different time periods in their life. For each event memory, participants will be asked to provide ratings regarding emotionality, vividness and other aspects of the memory. Sessions will be recorded to allow participant responses to be transcribed and scored at a later date. Participants are sent kits to collect blood spots, from which APOE E4 status will be identified.

Proposed One-Year and Long-Term Outcomes:

Building on studies already published in the Ryan and Grilli labs, the expanded study positions us for an R01 grant proposal to further explore the interactions between *APOE* E4 status and age-related alterations to episodic and semantic memory across the adult lifespan. We plan to present the results from the study at several conferences and publish the results in the coming year. We expect an R01 to be written and submitted in late 2026.

Year End Progress Summary:

Recruitment efforts for this study were supported by colleagues at TGen who utilized the online platform MindCrowd to recruit participants from across the lifespan in a targeted manner, allowing us to enrich the sample with APOE E4 carriers. Additionally, a significant subset of our study participants also took part in the Precision Aging Network's Healthy Minds for Life study, which includes a neuroimaging component.

As of June 30th, data collection for this project is now complete. A total of 166 participants ranging in age from 20 to 79 have been enrolled in the study, including 26 participants ages 20 to 29, 55 participants ages 40 to 59, and 85 participants ages 60 to 79. All participants have blood samples available for genotyping. With 28 samples still to be assayed, approximately one third of the sample are $\varepsilon 4$ carriers, allowing for analyses that will focus on both Specific Aims 1 and 2.

We have begun the process of transcribing the recorded testing sessions and are preparing to score and analyze the data this summer. Using a subset of the memories, we have established high interrater reliability for manual scoring (ICC > .85). In collaboration with Dr. Matt Grilli, we are now testing the use of a Large Language Model (LLM) for automated scoring of the memory narratives. The outcome of these test analyses will determine whether we implement the LLM or score all memory narratives manually. We intend to complete the scoring and analyses of the behavioral results for publication in Fall, 2026. Outcomes will be presented at several conferences in the coming year.

For the subset of participants who were recruited from the Healthy Minds for Life study, additional analyses are planned. We will conduct preliminary analyses focused on how episodic detail generation and semantic detail generation relate to the structural and functional connectivity of key brain regions involved in episodic and semantic memory, including medial temporal lobes regions. We aim to use these preliminary analyses in support of future grant applications.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Brain & Body Imaging Center Support. Lee Ryan, PhD, Nan-kuei Chen, PhD, Maria Altbach, PhD, Theordore Trouard, PhD, Elizabeth Hutchinson, PhD, Mary Ellen Koran, MD, PhD, Yi Su, PhD, Gene Alexander, PhD, Matthew Huentelman, PhD, Ashley Stokes, PhD, Kewei Chen, PhD. Psychology, University of Arizona; Biomedical Engineering, University of Arizona; Medical Imaging, University of Arizona; Radiology, Division of Nuclear Medicine, Mayo Clinic College of Medicine and Science; Banner Alzheimer's Institute; Translational Neuroscience, Barrow Neurological Institute; ASU-BNI Center for Preclinical Imaging; College of Health Solutions, Arizona State University; Translational Genomics Research Institute, Phoenix; Arizona Alzheimer's Consortium.

Specific Aims:

1. Enhance MRI capabilities for Large-Scale Research on aging and Alzheimer's Disease and related disorders. We plan to expand multi-site MR imaging capabilities to support large-scale, cutting-edge research on neurological disorders, including Alzheimer's disease to foster collaboration among researchers, physicians, and scientists across institutions in Arizona. The proposed MR imaging infrastructure will harmonize pulse sequences across clinical and preclinical MRI systems, establish platforms for data sharing and analysis pipelines to support cross-institutional collaborative center grants, enable the development and implementation of innovative MRI pulse sequences across platforms, and provide software support for analyzing large-scale, multi-modal imaging and non-imaging data, leveraging existing high-performance computing resources.

2. Advance Brain-Body Imaging Research for Human Health. Leveraging our expertise in multi-modal MR imaging—including neurological, cardiovascular, and liver MRI—we aim to identify brain-body imaging topics with the greatest impact on human health research. The proposed infrastructure will support new studies initiated by both established investigators and those expanding their research to incorporate innovative imaging tools at UofA and across Arizona.

3. Strengthen Training and Education in Imaging Science. Because the field of Brain and Body Imaging is constantly moving forward there is always an ongoing need for training and education in the latest techniques and applications. Our proposed infrastructure will play a key role in training by providing hands-on experience in collecting and analyzing multi-modal imaging and non-imaging data, organizing workshops and working groups on emerging neurological MRI topics, and hosting journal clubs and supporting trainee-driven research proposals. These activities will be made available through Zoom to sites throughout Arizona and beyond. Through these initiatives, we aim to cultivate a robust research and training ecosystem that advances imaging science throughout Arizona while securing vital funding to sustain and expand these efforts.

Background and Significance:

Funding from the Arizona Alzheimer's Consortium for the newly-established Brain & Body Imaging Center (BBIC) at the University of Arizona has supported the development and application of multi-modal imaging technologies, with a focus on Magnetic Resonance imaging (MRI), while training the next generation of scientists. The goal of the BBIC is to enhance infrastructure and provide technical and image analysis support for researchers throughout the Arizona Alzheimer's Consortium, enhancing collaborative research and supporting multi-site large scale research grants (e.g., U- and P-grants) as well as training grants (e.g., T-grants) that capitalize on our collective strengths in innovative clinical and preclinical MRI methods and large-data analytic approaches.

To enable multi-site imaging studies, BBIC will work across AAC sites to implement a unified set of advanced MRI pulse sequences across preclinical and clinical MRI systems from various vendors (e.g., Bruker, Siemens, GE, Philips). Harmonized imaging protocols would allow researchers to collect multicontrast MRI data using consistent methods across sites. We will work with our AAC partners to create a comprehensive suite of advanced MRI pulse sequences using the open-source Pulseq framework and vendor-specific interpreters. We will also expand UofA's growing library of MRI analysis pipelines and share large fully-annotated imaging datasets through an existing NIA-funded MRI data sharing sites.

BBIC will be a central resource for MRI design and analysis information that has the potential to greatly enhance aging and Alzheimer's-related research throughout the State of Arizona, as well as providing researcher resources and training for faculty, postdoctoral fellows, and graduate students. These activities complement the existing BAI Statistical and Image Analysis Resource, funded by AAC. BBIC has already demonstrated its utility through the services they provide to UofA researchers in Biomedical Engineering, Psychology, Medical Imaging, Physiology, Neurology, Psychiatry, Vascular Surgery, Neurosurgery, and Nursing. The ADRC Biomarker Core, led by Dr. Gene Alexander, has also benefitted from BBIC's expertise

Proposed One-Year and Long-Term Outcomes:

This is an important year for the newly established BBIC. We are supporting scientists and staff who will be developing protocols, procedures, and analysis pipelines that will support researchers throughout the AAC. Support from the AAC will assist in establishing the BBIC and for allowing it to expand beyond the University of Arizona. During this project period, we will coordinate efforts across laboratories throughout the state to make processing pipelines available and consistent across a variety of sites and platforms.

Year End Progress Summary:

During the past year, we held multiple online planning meetings with faculty at AAC sites across Arizona. We hired an administrative assistant for BBIC who is tasked with organizing meetings, contacting speakers, making travel arrangements, creating flyers, and ordering supplies for meetings, and maintaining the website. In September 2025, in partnership with the UofA's BIO5 Institute, we held a ribbon-cutting ceremony to celebrate the installation of two new state-of the art MRI scanners that was hosted by Dr. Tomas Diaz de la Rubia, Senior Vice President for Research and Partnerships, along with other UofA senior administrators, community and industry leaders, faculty, and trainees. Our distinguished speaker was Dr. Peter Bandettini (NIH), one of the foremost MRI researchers in the world.

To further promote research engagement, we created two speaker series. First, we organized faculty research forums to share expertise and generate research ideas, and a colloquium series featuring outstanding imaging national and international researchers. Second, we created **Tech Talks** – workshops where faculty share their expertise on cutting-edge imaging methods. These hands-on events, held at UofA and streamed online, were attended by 30-50 graduate students, postdoctoral fellows, and faculty, including colleagues from multiple institutions in Arizona (ASU, NAU, Mayo Clinic, Barrow Neurologic Institute, among others).

To further promote collaboration across our AAC sites in Arizona, we held a special research session at the AAC Annual Retreat (March, 2026, Show Low Arizona) focused on imaging research. This 4-hour event showcased 12 speakers from six AAC institutions who engage in all aspects of imaging research – from pulse sequence development to clinical application. The event was also an opportunity to plan a state-wide imaging research forum to be held at ASU in

Phoenix in October, 2026. The day-long event will be another opportunity to highlight the enormous wealth of expertise across Arizona and encourage multi-site collaborative grant development.

Speakers over the past year included:

Date	Event Type	Speaker Name	Topic/Title	Affiliation
September, 3, 2025	Distinguished Speaker	Peter Bandettini	What more might we do with fMRI? The challenge to better realize its limits and potential	NIH Center for Multimodal Neuroimaging
December 9, 2025	Tech Talk	Ted Trouard	The Structural Connectome of the Human Brain via Diffusion MRI	University of Arizona
January 28, 2026	Speaker Series	Corinne Pettigrew	Hidden Changes, Actionable Options: Biomarkers and Protective Factors in Early Alzheimer's Disease	Johns Hopkins University
February 16, 2026	Tech Talk	Vince Calhoun	Functional Connectivity	Georgia State University
February 16, 2026	Speaker Series	Scott Beeman	Exploring Tissue Microstructure and Metabolism with Quantitative MRI Approaches	Arizona State University
March 18, 2026	Speaker Series	Kristen Kennedy	Modifiers of healthy brain and cognitive aging and their implications for Alzheimer's related diseases	University of Texas Dallas
April 7, 2026	Tech Talk and Speaker Series	Qiuting Wen	Glymphatic MRI	Indiana University
April 15, 2026	Tech Talk	Dean Darnell	Innovations in MRI Hardware: Wireless, Portable and Reconfigurable Technologies for Advanced Neuroimaging	Duke University
April 20, 2026	Tech Talk	Ted Trouard	Fixel-Based Analysis	University of Arizona

Speakers at the AAC Annual Retreat (Show Low, Arizona, March 2026):

Oana Dumitrascu	Mayo Clinic
Matthew Huentelman	TGen
Yalin Wang	ASU
Mary Ellen Koran	Mayo Clinic
Lee Ryan	UofA
Nan-kuei Chen	UofA
Kewei Chen	ASU, Banner Alzheimer's Institute
Ted Trouard	UofA
Leslie Baxter	Barrow Neurological Institute/Mayo Clinic
Beth Hutchinson	UofA
Yi Su	ASU

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Cerebrovascular Contributions to Tau Pathways of Alzheimer's Disease Neurodegeneration. Bital Savir-Baruch, MD, Craig C. Weinkauf, MD, PhD, Juan C. Arias, MD. Department of Medical Imaging, Division of Nuclear Medicine, Division of Vascular Surgery, University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

1. **Evaluate Aβ and Tau brain accumulation in an at-risk cohort with CVD.** Leveraging our highly characterized CVD cohort, we will quantify AmyVid and TauVid (Lilly Inc.) by PET-CT in a total of 10 participants with elevated plasma pTau217 without dementia. **Hypothesis**: Cerebral Aβ deposition will be significantly less than tau; and, importantly, some of those tested will have increased tau accumulation with no Aβ. *Such data would run counter to AD dogma that presumes Aβ accumulation primacy, yet may explain historical data that contradicted these findings in some cohorts.*

Background and Significance:

Aβ plaques and NFTs are two neuropathologic hallmarks of AD.[1] CVD including cerebral small vessel disease, extracranial and intracranial large vessel disease have been associated with increased AD risk.[2, 3] An increasing body of literature indicates that AD and CVD affect the brain through different pathways of neurodegeneration.[4, 5] Several animal-based studies found an association between CVD and increased pTau expression independently of Aβ pathways. Qiu et al, using wild type and 3xTg-AD mice who underwent unilateral common-carotid artery ligation, found elevated pTau expression, as measured by western blot, in the brain cortex and hippocampus of both type of mice; in contrast, Aβ42 expression, determine by ELISA, was equal among groups.[6] Similarly, others found that CVD increased tau expression, as assessed by western blot and immunohistochemistry, in the hippocampus of (T44) transgenic mice who underwent bilateral common-carotid artery micro-coil placement.[7] Clinical studies have also explored the interplay between CVD and tauopathy. In a cohort of 600 subjects stratified by the Framingham general cardiovascular score, levels of cerebrospinal fluid (CSF) of total Tau and pTau181, but not Aβ42, were found significantly higher in subjects with high vascular risk after adjusting for age, sex, education, APOE4, and history of stroke.[8]

Although these pre-clinical and clinical data point to a CVD-related tau degeneration, Aβ42 and 40 immunoassays have been found less reliable than pTau assays. Upward drift has been reported in CSF Aβ 42 samples, reducing accuracy and reliability in predicting Aβ PET positivity.[9] This particular assay limitation questions whether CVD truly affects tau pathways or if this may be reflective of Aβ assays drifting. Similar limitations have been observed in Aβ42 and 40 plasma-based biomarkers. Ultimately, PET imaging remains as the gold standard for the quantification of Aβ and tau deposition in the brain.[10]

Preliminary Data:

Our previous published work, in collaboration with Dr. Beach and the Arizona Study of Aging and Neurodegenerative Diseases (AZSAND),[11] found that subjects with CVD have an increased tau burden independent of Aβ pathology.[12]

Experimental Design and Methods:

Study population and available plasma AD-biomarkers: A total of 10 subjects enrolled in the prospective Carotid and Mind (CAM) clinical study will be used for this analysis. We will test these participants for pTau217 (abnormal defined as >0.42 pg/dL) and ensure they have no evidence of clinical dementia as defined by NACC normative MoCA <2.0 SD and no deficit in performing activities of daily living. Blood is drawn in all study participants to quantify plasma pTau-217, Aβ42/40 and apolipoprotein E allele 4 (APOE4) genotypes through collaboration with the Biomarker Assay Laboratory at the National Centralized Repository for Alzheimer's Disease (NCRAD). Study patients will need to be screened and further optimized based on brain morphometry, blood-brain barrier integrity, and blood biomarker evaluation to ensure a highly selected cohort of 10 patients optimized for detecting AmyVid vs TauVid differences. Our goal is to identify a optimized cohort of 10 individuals with highest pTau217 and other features that we hypothesize are potentially associated with PET-based tau/amyloid brain changes. This is critical because we are only performing PET scans on 10 patients.

AD PET biomarkers: PET/CT will be performed to quantify Aβ and tau brain deposition. Scans will be conducted using the GE Discovery MI Digital PET/CT system (Boston, Massachusetts) with dynamic imaging at 2 seconds per frame. Each PET scan will be performed during a separate visit. All images will be collected according to the standard of practice, including 0.1 mCi/kg up to 14.0 mCi of FDG, 10 mCi of AmyVid, and TauVid. After the I.V. injection of the tracer, images will be obtained at 45 minutes and 80 minutes post-injection for AmyVid and TauVid, respectively (Eli Lilly). AmyVid and TauVid scans will be analyzed by clinical evaluation and also using MIM software (recently FDA approved, GE) to calculate standardized uptake value ratios (SUVR). We will evaluate both regional and whole brain patterns of change.[13-16]

Statistical analysis: Prevalence of positive and negative Aβ and tau deposition will be calculated based on standard cut-offs of tracer SUVR. To evaluate the relationship between Aβ and PET uptake and Aβ42/40 ratios a Pearson correlation coefficient will be calculated to determine the strength and direction of their linear association. Similar analysis will be run pTau217/ Aβ40, pTau217/Aβ42 ratios and Aβ PET uptake values.

Proposed One-Year and Long-Term Outcomes:

One-year outcomes: Selection of optimized study participants will be scanned with MRI and tested for pTau217. After optimization of the cohort based on pTau217 levels and brain imaging parameters, we will perform PET imaging with AmyVid and TauVid tracers in collaboration with Lilly. Images will be postprocessed and interpreted by a neuroradiologist. Postprocessed data will be analyzed according to the statistical plan. Results will be shared with the scientific community at conferences and through peer-review publications. **Long-term outcomes:** These data will fuel future R01 grant applications aiming to better understand CVD contributions to Aβ and tau PET biomarkers of AD.

Year End Progress Summary:

Although there has been significant difficulty obtaining and finalizing contracts with Lilly to supply and use TauVid and AmyVid tracers for the project, we have made excellent progress. This project cannot be completed without Lilly support (because tracers cost roughly $65,000 or more, which is far more than what the AAC budget allows). However, we have ensured adequate funds through Lilly to compete the project. We have now completed the UA/Lilly contract and are awaiting finalization of signatures.

In the meantime, we used the AAC funds to optimize selection of the 10-patient cohort through performing MRI and comparison of brain morphometry (Figure 1) to pTau217, Aβ42/40, and neurocognitive testing as planned. Using the funding from this grant, we were able to screen roughly 40 participants with the goal of selecting an optimized group of 10 patients for PET imaging (Table 1). We also submitted two RO1 grants related to this work and are awaiting final data for an additional RO1 submission.

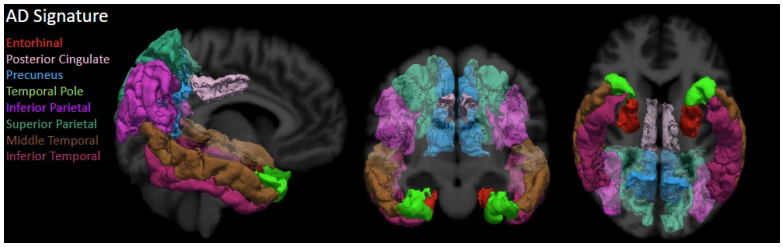


Fig. 1) Visualization of the AD Signature brain regions. CAM morphometrics were derived from T1 images using FreeSurfer v7.3.2 with the standard pipeline The AD signature region was defined using the FreeSurfer Desikan-Killiany atlas. Primary measures included cortical surface area, thickness, andSA, cTH and volume.

Table 1: List of CAM Participants Screened for PET

Subject ID	Plasma ALZPath pTau217 (pg/mL)	Plasma Ab42/40	MoCA Score	Carotid Cognitive Index	AD Signature Surface Area (cm2)	AD Signature Thickness (cm)	Hippocampal Volume (cm3)
CAM076	2.23	0.057	20	-0.92	498.2	2.54	508.5
CAM107	1.98	0.060	24	-0.37	539.8	2.46	572.4
CAM125	1.59	0.057	27	-1.16	525.5	2.57	613.6
CAM146	1.48	0.052	25	0.08	540.5	2.47	705.5
CAM105	1.38	0.054	23	-0.17	473.1	2.55	526.9
CAM172	1.38	0.047	25	-0.51	560.7	2.70	594.5
CAM163	1.11	0.051	21	0.33	492.6	2.77	614.3
CAM133	1.06	0.057	16	-1.37	543.5	2.53	501.2
CAM152	1.03	0.063	25	-0.30	437.7	2.55	628.0
CAM159	0.99	0.047	27	0.13	533.7	2.63	587.9
CAM042	0.98	0.073	28	0.89	574.3	2.74	646.3
CAM017	0.89	0.055	24	0.59	524.7	2.93	664.8
CAM137	0.85	0.060	19	0.21	510.1	2.57	613.5
CAM151	0.83	0.055	23	0.51	560.8	2.66	637.5
CAM038	0.82	0.062	18	-1.06	527.6	2.49	584.3
CAM112	0.8	0.064	20	0.01	530.4	2.58	589.5
CAM086	0.79	0.026	23	-1.10	493.7	2.69	637.4
CAM036	0.77	0.056	28	-0.23	556.9	2.57	577.0
CAM115	0.73	0.071	21	-0.03	525.5	2.53	584.6
CAM066	0.72	0.057	26	0.17	568.4	2.73	674.4
CAM095	0.72	0.065	26	0.97	545.6	2.82	636.7
CAM136	0.72	0.049	21	-0.34	512.3	2.58	547.2
CAM078	0.69	0.072	25	-0.78	557.3	2.59	557.5
CAM117	0.69	0.028	26	0.20	467.6	2.82	496.5
CAM174	0.69	0.062	20	-0.63	587.1	2.51	647.9
CAM084	0.68	0.054	15	-0.86	568.2	2.74	652.3
CAM131	0.66	0.059	19	-0.63	588.9	2.48	686.7
CAM077	0.65	0.084	17	-2.05	457.0	2.45	557.8
CAM129	0.61	0.071	22	0.70	525.6	2.74	742.4
CAM138	0.61	0.055	21	-0.85	540.0	2.65	566.8
CAM004	0.58	0.093	25	-1.22	505.9	2.46	554.9
CAM171	0.55	0.057	24	0.00	583.5	2.61	616.9
CAM009	0.54	0.068	28	-0.04	535.0	2.53	641.1
CAM014	0.54	0.064	28	1.38	516.4	2.74	619.8
CAM064	0.54	0.066	23	0.54	466.3	2.61	552.9
CAM119	0.54	0.053	27	1.31	534.2	2.63	688.9
CAM096	0.53	0.071	25	1.29	617.8	2.76	670.2
CAM011	0.52	0.065	21	0.51	586.0	2.59	658.0
CAM045	0.52	0.067	23	0.81	511.1	2.47	533.2
CAM070	0.51	0.035	21	-0.80	497.1	2.52	677.6

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Targeting Parthanatos to mitigate inflammatory responses via gut-brain axis in AD. Mehtab Shaik, PhD. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

Aim 1: To evaluate the role of global and intestinal-specific knockout of Parp1 on the temporal association of Aβ amyloid deposition and neuroinflammation. To distinguish the contribution of the gut mucosal PARylation to the progression of amyloid pathology and PARylation in the CNS, I plan to utilize male and female WT mice, 3xTg mice, and 3xTg with intestinal epithelial cell-specific Parp1 knockout (3xTg-Parp1$^{\Delta IEC}$). Mice will be euthanized at 3-, 6-, and 12-months of age to capture (1.1) the disease progression (1.2) intestinal permeability, and (1.3) Spatial transcriptomics.

Aim 2: To test the role of PARP1 in modulating neuroinflammation induced by AD microbiome. GF or antibiotic (Abx) pre-cleared WT, 3xTg and 3xTg-Parp1$^{\Delta IEC}$ mice will be colonized by fecal bacteria from healthy and AD patients followed by (2.1) the histological analysis of Aβ levels, and PARylation, (2.2) Spatial transcriptomics (2.3) microbiome analysis (2.4) serum metabolomics (2.5) inflammatory markers of gut and brain, intestinal epithelial barrier (IEB) and blood-brain barrier (BBB) permeability.

Background and Significance:

Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by synaptic loss, neuronal death, and the accumulation of amyloid-β plaques and neurofibrillary tau tangles. In addition to these classical hallmarks, neuroinflammation has emerged as a central driver of disease progression, mediated by cytokines, chemokines, and reactive oxygen and nitrogen species produced by central and peripheral immune cells. Recent studies further implicate the gut microbiome as a key modulator of neuroinflammatory processes in AD, with patients and animal models exhibiting shifts toward proinflammatory microbial communities. Experimental manipulation of the microbiota has been shown to influence amyloid pathology, highlighting the importance of the Brain-Microbiota-Gut (BMG) axis in AD pathogenesis.

Despite advances in understanding AD, the mechanisms underlying neuronal cell death remain incompletely defined. Emerging evidence identifies Parthanatos, a PARP1-dependent, NAD^+-depleting form of programmed cell death, as a critical contributor to neurodegeneration. Hyperactivation of PARP1 in response to oxidative stress, inflammation, and microbial toxic metabolites leads to excessive PARylation, mitochondrial dysfunction, and energy failure, ultimately triggering neuronal death. Notably, PARP1 has also been linked to inflammatory signaling and may function as a sensor of microbiome-derived signals. However, the role of PARP1 in integrating microbiome dynamics with neuroinflammatory and neurodegenerative processes in AD remains largely unexplored.

This gap is significant because AD is increasingly recognized as a multifactorial disease involving complex interactions between central and peripheral systems. Understanding how PARP1-mediated pathways connect gut microbiota alterations to neuroinflammation and neuronal loss could reveal novel mechanisms driving disease progression. Such insights have strong translational potential, as pharmacological PARP inhibitors and microbiome-targeted interventions may offer new strategies to mitigate neuroinflammation and promote neuroprotection. Together, this work aims to advance a more integrated view of AD pathogenesis and identify actionable targets for disease-modifying therapies.

Preliminary Data, Experimental Design and Methods:

Our preliminary data shows that PARP1 activity in the gut is highly dependent on the composition of the microbiota. Germ-free (GF) mice exhibit no detectable PARylation, while antibiotic treatment in SPF mice markedly reduces it. Recolonization of GF mice with specific pathogen free microbiota restores PARylation demonstrating that commensal microbes directly regulate PARP1 activity. This effect is completely absent in $Parp1^{-/-}$ mice, confirming the role of PARP1 in mediated PARylation.

In Alzheimer's Disease, PARP1 is activated by oxidative stress and Aβ, and in turn can further promote Aβ deposition and tau pathology, positioning it both upstream and downstream of disease processes. Consistent with this, 3xTg AD mice show elevated PARP1 expression and PARylation in both the brain and colon compared to wild-type controls, highlighting a previously underexplored role of PARP1 in the gut in AD. Notably, female AD mice exhibit relatively higher PAR levels than males, suggesting sex-dependent differences.

Additionally, increased expression of apoptosis-inducing factor (AIF) in the colon of AD mice indicates enhanced susceptibility to PARP1-mediated cell death (Parthanatos) and potential gut epithelial dysfunction, particularly in regions with high microbial density. Subtle sex- and region-specific differences in AIF expression further support a sexually dimorphic response. Overall, these findings suggest that microbiota-driven PARP1 activation may link gut alterations to neuroinflammation and neurodegeneration through the brain-microbiome-gut axis in AD.

Proposed One-Year and Long-Term Outcomes:

The short-term outcome of this project is anticipated to establish foundational evidence linking PARP1 hyperactivation to neuroinflammation through the BMG axis in AD. Specifically, we expect demonstrating that Aβ-induced oxidative stress drives hyperPARylation and activates the Parthanatos pathway wherein PARP1-mediated hyperactivity drives nuclear translocation of AIF–MIF complex, contributing to neuronal death and microglial activation in 3xTg mouse models. Comparative analyses of transcriptomic profiles from 3xTg, and 3xTg-$Parp1\Delta^{IEC}$ mice, alongside microbiome and metabolite profiling, will identify key dysregulated pathways associated with Parp1-mediated inflammation and neurodegeneration.

In the long term, this research aims to redefine the understanding of AD pathogenesis and the mechanisms of neuronal cell death leading to neurodegeneration. By establishing how dysbiotic microbiome contributes to PARP1-mediated Parthanatos and its role in mediating the inflammatory responses across the brain–gut axis we will uncover peripheral molecular player as critical drivers of neuroinflammation and disease progression. This work has the potential to enable the development of precision medicine approaches that integrate neuroinflammatory, genetic, and microbiome-based biomarkers for early diagnosis and targeted treatment.

Year End Progress Summary:

We obtained 3xTg mice on B6 background [B6.Cg.Tg(APPSwe,tauP301L) LfaPsen1tm1Mpm/2J along with WT C57BL/6 controls from The Jackson Laboratory. Breeding colonies have been established by crossing 3xTg with intestinal epithelial Parp1 knockout mice ($Parp1^{\Delta IEC}$) mice to generate 3xTg-$Parp1^{\Delta IEC}$ animals. These mice cohorts are currently maintained and will be used for tissue collection at defined ages to assess changes in PARylation and amyloid pathology.

2. Fecal samples are being collected longitudinally from male and female 3xTg and WT mice at multiple timepoints to enable temporal analysis of microbiome and to characterize the progression toward dysbiosis in 3xTg AD mice.

3. 16S RNA sequencing has been performed on fecal samples collected from 3xTg mice at 6-month and 12-months of age. These microbiotas have been used for fecal microbial transplantation into germ-free (GF) mice. Brain, gut, serum and cecal tissue have been collected following 12 wks. and 18 wks. of colonization from these Ex-GF mice.

4. Brain and colon tissues harvested from Ex-GF mice colonized with fecal samples collected from 3xTg mice or WT mice is currently being processed for transcriptomic analysis.
5. Immunofluorescence assays are being conducted to assess the levels of PARylation in the brain as well as in the colonic tissues and to evaluate nuclear translocation of AIF and MIF from mitochondria, with the aim of investigating the activation of the Parthanatos pathway.

Key findings and Challenges:
Immunofluorescence analysis of brain and colon tissues demonstrates a consistent upregulation of PARP1 and PARylation in 3xTg mice compared to controls at both 6-month and 12-month time points. The persistence of elevated PARP1 signaling over time reflects ongoing DNA damage responses, chronic cellular stress, and impaired genomic maintenance associated with AD pathology. Importantly, the effect is more pronounced in female mice, indicating a clear sex-dependent vulnerability in PARP1 activation and downstream PARylation. This finding is particularly significant because it aligns with known epidemiological trends showing higher AD prevalence and severity in females. It suggests that sex-specific biological mechanisms potentially involving hormonal regulation, mitochondrial function, or differential DNA damage responses may amplify PARP1 pathway dysregulation in females. The observation of increased PARP1 and PARylation in both brain and colon tissues also raises the possibility of a systemic component to AD-associated molecular changes, supporting the idea of a gut–brain axis involvement in disease pathology. Overall, these findings highlight PARP1-mediated PARylation as a robust, time-dependent, and sex-influenced molecular signature of Alzheimer's pathology with potential implications for both mechanistic understanding and therapeutic intervention.

Two key challenges were encountered during the initiation of the project. First, for aim1 there have been delays in establishing the necessary account and logistical arrangements with The Jackson Laboratory to obtain the 3xTg-AD mouse line. This has slowed the timeline for generating the required experimental cohorts, particularly the breeding strategy involving crosses with the $PARP1^{\Delta IEC}$ (Parp1 KO) line. Second, there has been difficulty in securing access to human stool samples from Alzheimer's disease patients for use in fecal microbiota transplantation (FMT) studies required for aim2. This limitation restricts the ability to directly model AD-associated gut microbiome alterations and evaluate their functional impact *in vivo.*

As an alternative strategy, fecal material from 12-month-old 3xTg mice was used to prepare slurries for FMT into germ-free (GF) mice. GF mice were colonized at 10 weeks of age with microbiota derived from either wild-type (WT) or 3xTg donor mice. Following transplantation, mice were maintained for 12 or 18 weeks to allow for stable microbial engraftment. At the end of the experimental period, brain and gut tissues were harvested for downstream analyses. Current investigations are focused on assessing PARylation status as a marker of PARP1 pathway activity, alongside brain metabolomic profiling to evaluate systemic and neurochemical alterations. In parallel, microbiome analyses are being conducted to characterize donor-derived microbial composition and its persistence over time in recipient mice. We anticipate obtaining results from aim2 within the next six months.

Together, these challenges highlight key logistical and resource-dependent bottlenecks in the study, affecting both the in vivo genetic model development and the translational microbiome component of the project.

Next step:
Collaborations are essential to obtain clinically relevant samples and ensure sufficient statistical and biological power for microbiome-related experiments. To address this, I have established active collaboration with Dr. Emily Cope at Northern Arizona University and initiated experiments to investigate Parthanatos in 3xTg mice across different ages.

At the recent Alzheimer's Association Consortium annual retreat, I met with Drs. Jessica Langbaum and Alireza Atri to discuss potential collaboration opportunities for obtaining stool

samples from patients clinically diagnosed with AD. With continued funding support from ADRC following the first-year progress evaluation, we will have the resources to initiate these collaborations and begin collecting the clinically relevant samples.

The continued support of ADRC development grant for an additional year will enable the successful evaluation of how Alzheimer's disease-associated microbiota influence host molecular pathways, particularly PARP1-mediated signaling, while also providing a strong foundation for securing funding from NIH (R21 and RO1 submission planned).

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Advancing Plasma-Based Detection of Alzheimer's Disease Biomarkers Using FLOWER.
Judith Su, PhD, Gene Alexander, PhD, Thomas Beach, MD, PhD. University of Arizona (Tucson); Arizona Alzheimer's Consortium; Banner Sun Health Research Institute.

Specific Aims:
The specific aim of this project is to quantify ptau217 levels in plasma from patient samples provided by the Brain and Body Donation Program (BBDP). This will be done using an ultra-sensitive optical sensing technique known as FLOWER[1,2], which we have developed in our lab.

Background and Significance:
We have developed a technique known as FLOWER that can detect zeptomolar concentrations of molecules without requiring labels such as fluorescent or radioactive tags.[3] We are currently evaluating FLOWER's ability to detect Alzheimer's disease (AD) biomarkers, specifically amyloid beta and tau, in cerebrospinal fluid (CSF) and plasma. In a previous AAC-funded pilot, we used FLOWER to detect amyloid beta and tau in cadaveric CSF and serum, distinguishing between diagnostic groups in CSF but not in serum, possibly due to biomarker degradation post-mortem (Gin et al, *npj Biosensing* 2024). In the current project, we are analyzing prospectively collected plasma from BBDP participants drawn within 18 months of death. These higher-quality samples are expected to yield clearer results. **While techniques such as SIMOA have demonstrated the detection of AD biomarkers in serum, they have not yet reliably distinguished individuals with mild cognitive impairment (MCI), making the development of ultra-sensitive sensors a critical priority.**

Preliminary Data:
Using FLOWER, we are able to measure levels of Aβ42 in CSF and distinguish between control subjects, patients diagnosed with mild cognitive impairment, and those with AD (Gin et al, *npj Biosensing* 2024))

Experimental Designs and Methods:

- **Microtoroid Fabrication:** As previously described, microtoroids are fabricated using photolithography, XeF_2 etching, and CO_2 laser reflow to achieve ultra-high-Q optical resonators.

- **Surface Functionalization:** Toroids are silanized using APTES, then functionalized via EDC/NHS chemistry to attach anti-ptau217 antibodies.

- **Sensing Experiments:** We have now received the BBDP plasma samples, and a newly trained student is actively working on these experiments. Plasma samples are diluted 10× with PBS, centrifuged, and incubated with anti-ptau217-functionalized microtoroids for 2.5

hours. After washing, secondary anti-ptau217 is perfused while recording WGM resonance shifts.

The maximum resonance shift is calculated by exponential curve fitting, and results are visualized using box plots for each diagnostic group. Each group contains ~30 samples.

Standard evanescent coupling using a tapered optical fiber is employed. Resonance dips are tracked in real time using a photodetector.

Proposed One-Year and Long-Term Outcomes:

Over the next year, we will complete the analysis of plasma samples and begin statistical assessment of FLOWER's diagnostic capabilities. Long-term, we plan to develop multiplexed assays and advance toward clinical trials to validate FLOWER as an early detection and monitoring tool for Alzheimer's disease.

Year End Progress Summary:

During the reporting period, we evaluated the feasibility of using FLOWER to detect Alzheimer's disease biomarkers in prospectively collected plasma samples from the Brain and Body Donation Program. Our findings suggest that achieving robust plasma-based diagnosis will likely require multiplexed detection of multiple complementary biomarkers rather than reliance on a single biomarker, guiding the next phase of assay development.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Brain & Body Imaging Center Support. Theodore Trouard, PhD, Lee Ryan, PhD, Nan-kuei Chen, PhD, Maria Altbach, PhD. Biomedical Engineering, University of Arizona; Psychology, University of Arizona; Medical Imaging, University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

1. Enhance MRI capabilities for Large-Scale Research on aging and Alzheimer's Disease and related disorders.

We plan to expand multi-site MR imaging capabilities to support large-scale, cutting-edge research on neurological disorders, including Alzheimer's disease to foster collaboration among researchers, physicians, and scientists across institutions in Arizona. The proposed MR imaging infrastructure will enable the development and implementation of innovative pulse sequences across platforms, provide software support for analyzing large-scale imaging data, and establish platforms for cross-institutional collaboration to co-develop large-scale center grants with a focus on generating compelling preliminary data.

2. Advance Brain-Body Imaging Research for Human Health.

Leveraging our expertise in multi-modal MR imaging—including neurological, cardiovascular, and liver MRI—we aim to identify brain-body imaging topics with the greatest impact on human health research. The proposed infrastructure will support new studies initiated by both established investigators and those expanding their research to incorporate innovative imaging tools at UofA and across Arizona.

3. Strengthen Training and Education in Imaging Science.

Because the field of Brain and Body Imaging is constantly moving forward there is always an ongoing need for training and education in the latest techniques and applications. Our proposed infrastructure will play a key role in training by providing hands-on experience in collecting and analyzing multi-modal imaging and non-imaging data, organizing workshops and working groups on emerging neurological MRI topics, and hosting journal clubs and supporting trainee-driven research proposals. These activities will be made available through Zoom to sites throughout Arizona and beyond. Through these initiatives, we aim to cultivate a robust research and training ecosystem that advances imaging science throughout Arizona while securing vital funding to sustain and expand these efforts.

Background and Significance:

The Brain & Body Imaging Center (BBIC) supports the development and application of multi-modal imaging technologies, with a focus on Magnetic Resonance imaging (MRI), while training the next generation of scientists. The goal of the BBIC is to enhance infrastructure and provide technical and image analysis support for researchers throughout the Arizona Alzheimer's Consortium, enhancing all research and leading to large-scale collaborative research grants (e.g., U- and P-grants) as well as training grants (e.g., T-grants) that capitalize on innovative MRI methods and large-data analytic approaches.

At the University of Arizona, more than half of the AAC pilot project grants include MR or other imaging modality. These pilot grants have been supported by BBIC researchers and personnel, including Drs. Ted Trouard, Nan-kuei Chen, Maria Atlbach, Lee Ryan, Chidi Ugonna, and others. This research has led to multiple extramurally funded grants totaling more than $10M in new grants over the past two years, and contributed to the success of the current NIA-funded U19 Precision Aging Network (Barnes, PI).

Building on the success of the NIH U19-funded Precision Aging Network, we plan to expand MR imaging capabilities to support large-scale, cutting-edge research on neurological disorders, including Alzheimer's disease. This expansion will foster collaboration among researchers, physicians, and scientists across institutions in Arizona.

Proposed One-Year and Long-Term Outcomes:

This is an important year for the newly established Brain & Body Imaging Center. We are supporting scientists and staff who will be developing protocols, procedures, and analysis pipelines that will support researchers throughout the AAC. Support from the AAC will assist in establishing the BBIC and for allowing it to expand beyond the University of Arizona. During this project period, we will coordinate efforts across laboratories throughout the state to make processing pipelines available and consistent across a variety of sites and platforms.

Year End Progress Summary:

During the past year, we held multiple online planning meetings with faculty at AAC sites across Arizona. We hired an administrative assistant for BBIC who is tasked with organizing meetings, contacting speakers, making travel arrangements, creating flyers, and ordering supplies for meetings, and maintaining the website. In September 2025, in partnership with the UofA's BIO5 Institute, we held a ribbon-cutting ceremony to celebrate the installation of two new state-of the art MRI scanners that was hosted by Dr. Tomas Diaz de la Rubia, Senior Vice President for Research and Partnerships, along with other UofA senior administrators, community and industry leaders, faculty, and trainees. Our distinguished speaker was Dr. Peter Bandettini (NIH), one of the foremost MRI researchers in the world.

To further promote research engagement, we created two speaker series. First, we organized faculty research forums to share expertise and generate research ideas, and a colloquium series featuring outstanding imaging national and international researchers. Second, we created **Tech Talks** – workshops where faculty share their expertise on cutting-edge imaging methods. These hands-on events, held at UofA and streamed online, were attended by 30-50 graduate students, postdoctoral fellows, and faculty, including colleagues from multiple institutions in Arizona (ASU, NAU, Mayo Clinic, Barrow Neurologic Institute, among others).

To further promote collaboration across our AAC sites in Arizona, we held a special research session at the AAC Annual Retreat (March, 2026, Show Low Arizona) focused on imaging research. This 4-hour event showcased 12 speakers from six AAC institutions who engage in all aspects of imaging research – from pulse sequence development to clinical application. The event was also an opportunity to plan a state-wide imaging research forum to be held at ASU in Phoenix in October, 2026. The day-long event will be another opportunity to highlight the enormous wealth of expertise across Arizona and encourage multi-site collaborative grant development.

Speakers over the past year included:

Date	Event Type	Speaker Name	Topic/Title	Affiliation
September, 3,2025	Distinguished Speaker	Peter Bandettini	What more might we do with fMRI? The challenge to better realize its limits and potential	NIH Center for Multimodal Neuroimaging
December 9, 2025	Tech Talk	Ted Trouard	The Structural Connectome of the Human Brain via Diffusion MRI	University of Arizona
January 28, 2026	Speaker Series	Corinne Pettigrew	Hidden Changes, Actionable Options: Biomarkers and Protective Factors in Early Alzheimer's Disease	Johns Hopkins University
February 16, 2026	Tech Talk	Vince Calhoun	Functional Connectivity	Georgia State University
February 16, 2026	Speaker Series	Scott Beeman	Exploring Tissue Microstructure and Metabolism with Quantitative MRI Approaches	Arizona State University
March 18, 2026	Speaker Series	Kristen Kennedy	Modifiers of healthy brain and cognitive aging and their implications for Alzheimer’s related diseases	University of Texas Dallas
April 7, 2026	Tech Talk and Speaker Series	Qiuting Wen	Glymphatic MRI	Indiana University
April 15, 2026	Tech Talk	Dean Darnell	Innovations in MRI Hardware: Wireless, Portable and Reconfigurable Technologies for Advanced Neuroimaging	Duke University
April 20, 2026	Tech Talk	Ted Trouard	Fixel-Based Analysis	University of Arizona

Speakers at the AAC Annual Retreat (Show Low, Arizona, March 2026):

Oana Dumitrascu	Mayo Clinic
Matthew Huentelman	TGen
Yalin Wang	ASU
Mary Ellen Koran	Mayo Clinic
Lee Ryan	UofA
Nan-kuei Chen	UofA
Kewei Chen	ASU, Banner Alzheimer’s Institute
Ted Trouard	UofA
Leslie Baxter	Barrow Neurological Institute/Mayo Clinic
Beth Hutchinson	UofA
Yi Su	ASU

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Physiologic Pathways Associated with Neurodegeneration in the Vascular Population. Craig C. Weinkauf MD, PhD, Scott R. French, BS, Juan C. Arias, MD. Division of Vascular Surgery; University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

1. Endothelial damage and blood brain barrier (BBB) breakdown are elevated in the vascular population as measured by the NULISA CNS Panel.
2. Endothelial damage and BBB breakdown correlate with AD pathology.
3. NULISA Argo CNS Panel pTau-217 levels show high concordance with Quanterix HD-X pTau-217.

Background and Significance:

Some early features of Alzheimer's disease and related dementias (ADRD) are associated with vascular diseases, including asymptomatic extracranial carotid artery disease (aECAD). Prior work done in our lab found that aECAD is associated with 22-48% increased ADRD risk[1] and neurofibrillary tangle (NFT) accumulation.[2] Despite these data, aECAD patients and the vascular population are not regularly evaluated for cognitive health in the clinic, potentially due to a lack of understanding of how vascular and neurodegenerative pathways interact in ADRD development. Using a broad spectrum of blood biomarkers available through the NULISA Argo HT CNS panel, we sought to evaluate specific physiologic pathways that may be relevant to ADRD risk in a unique, highly characterized cerebrovascular cohort.

Preliminary Data, Experimental Design and Methods:

In our ongoing, prospective CAM study evaluating long-term ADRD risk in a cerebrovascular cohort (≥2 vascular risk factors with or without aECAD and no clinical diagnosis of mild cognitive impairment or dementia), 30% have neurocognitive test scores in agreement with clinically significant cognitive impairment after adjusting for age, sex, and education. Additionally, 60% have elevated plasma pTau-217 according to established cutoffs.[3,4] This degree of cognitive impairment and abnormal pTau-217 exceeds what has been observed in other cohorts representative of the general population,[3-6] indicating that this vascular population has elevated AD risk. Based on this preliminary data, we wanted evaluate specific physiologic pathways that may be relevant to ADRD risk in this unique patient population.

Participants in our ongoing longitudinal CAM study had plasma drawn and banked with the University of Arizona Biorepository. CAM participants are men and women between the ages of 50-85 with ≥2 cardiovascular risk factors with or without aECAD. Cardiovascular risk factors are defined as hypertension, hyperlipidemia, smoking (current or >10 pack-years), and diabetes. Exclusion criteria include a history of stroke/transient ischemic attack within 6 months prior to enrollment, previous clinical diagnoses of TBI, cognitive impairment, dementia or neurological diseases, and/or terminal cancer. In addition, plasma samples matched for age, sex, education, race and ethnicity will be purchased from the ADRC-NACC catalog at NCRAD. Exclusion criteria include samples collected postmortem, missing APOE genotype/pTau-217, interval between cognitive testing and plasma collection >30 days, and prior diagnoses of TBI, psychiatric diseases, and/or neurological diseases. Plasma samples will be analyzed at Banner Sun Health Research Institute using the NULISA Argo CNS Panel. If NACC samples are not available, we will instead evaluate pre-surgery vs. post-surgery samples from CAM as a method for further understanding vascular risk in this patient population and the potential benefit of an intervention.

NULISA panel biomarker data will be normalized into NULISA protein quantification units by dividing the target counts by internal control counts of each well and then by the median IPC counts, followed by log_2 transformation as previously described.[7,8] The strength and direction of relationships between plasma pTau-217 and biomarkers from the NULISA Argo HT CNS panel, including biomarkers of endothelial activation and BBB damage, will be explored in each cohort using linear regression analyses with the following adjustments: 1) unadjusted; 2) age, sex; 3) age, sex, education; 4) age, sex, education, race, ethnicity; 5) age, sex, education, race, ethnicity, APOE4; 6) age, sex, education, race, ethnicity, APOE4, vascular risk factors/diseases. The regression models will be repeated with adjusted MoCA scores as the outcome. Participants in each cohort (separate and combined) will be split into groups based on their pTau-217 status using established cutoffs.[3] Biomarker concentrations will be compared between each group using Mann Whitney U tests (with and without FDR-correction)[9] and logistic regression models will be used to adjust for potential confounding factors. The extent of endothelial activation, BBB damage, cognitive impairment, and AD pathology will be compared between the cerebrovascular (CAM) and non-vascular (NACC-ADRC) cohorts using Mann Whitney U tests and Fisher's Exact tests and will be further adjusted for confounders using regression models. Concordance between NULISA and Quanterix HD-X pTau-217 will be evaluated using Spearman's correlation and Bland-Altman tests.

Proposed One-Year and Long-Term Outcomes:

One-Year outcomes: Upon notification of acceptance, we will send ~314 samples via overnight shipping on dry ice to Banner Sun Health Research Institute to run the NULISA Argo HT CNS panel; these results will be compared to pTau-217, MoCA and other ADRD outcomes. We plan to submit a manuscript for publication within the same calendar year. **Long-term outcomes:** R01 grant submission to further investigate vascular-related pathways of neurodegeneration.

Year End Progress Summary:

After notification of acceptance, we prepared CAM samples for shipment to Banner Sun Health Research Institute. We submitted a sample request to NCRAD to purchase the NACC/ADRC samples. The sample request process from NCRAD required increased time because of contracts with the UA/NACC and it was clear that this was going to take far more time than expected.

This enabled us to focus on the pre-surgery vs post-surgery strategy for analysis of CAM samples. As such, we sent plasma samples (N=230 baseline and N=133 1-year follow-up visits) were pulled from the UA Biorepository and sent to Banner Sun Health Research Institute for the NULISA Argo HT CNS panel. Due to additional support from the AAC Biomarker Measurement Support grant, these samples also had the NULISA Inflammation panel, which measures 250 inflammatory proteins simultaneously with high sensitivity and specificity. We currently have NULISA Argo HT CNS panel data available in 159 participants, 82 of which have follow-up. The remaining NULISA CNS panel and NULISA Inflammation panels are currently being run by Banner Sun Health Research Institute.

In addition to the progress made in our pre/post analyses, we were able to complete our "added-value" Aim 3 within the CAM cohort. Our data suggests that NULISA CNS panel biomarkers have strong concordance with biomarkers measured using Quanterix Simoa (pTau217, NFL, GFAP, Ab40, Ab42), ELISA (PDGFRb, VCAM-1, CRP, YKL40, BDNF), and Luminex (S100B, KLK6, SNCA, VEGFA). Notably, the NULISA panel was able to measure low abundance proteins (TNFa and PLGF) that were unable to be detected in our samples using Luminex assays, demonstrating the high sensitivity associated with NULISA. Overall, our data indicates that NULISA assay results are highly consistent with traditional assay formats but provide notably higher sensitivity.

We are also performing additional analyses that were not explicitly mentioned in the original proposal. For example, we found that plasma eotaxin levels correlate strongly with cognitive impairment in patients with carotid disease. Adding eotaxin to a multivariable logistic regression model alongside plasma pTau217 and demographic factors increases AUC for detecting cognitive impairment in the aECAD population, reaching a maximum AUC of 0.85 for MoCA <26 and 0.93 for MoCA <18 (Figure 1). These data are particularly relevant as carotid disease is treatable with CEA, but these patients are not currently being evaluated or treated for brain health outcomes which we think is due to a lack of accurate clinical tools to stratify neurodegenerative risk in this patient population. We are working toward preparing a manuscript for submission to the Journal of Vascular Surgery outlining these findings. We are also using this as preliminary data for a future grant submission that will allow us to perform unbiased proteomics with the Somascan 11K assay on all CAM participants.

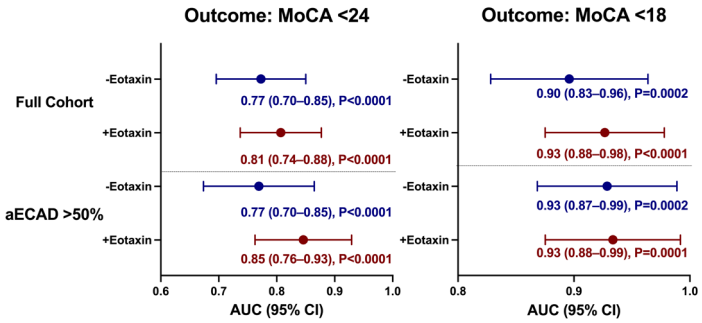


Figure 1: Plasma eotaxin detected with NULISA increases diagnostic accuracy of pTau217 and demographic factors for detection of cognitive impairment.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Identify Predictive Biomarkers for Carotid Intervention-Related Microembolization. Wei Zhou, MD, Theodore Trouard, PhD, Nesam Haider, PhD, Chiu-Hsieh Hsu, PhD, Jose Elchieveri, MD. Department of Surgery; Department of Biomedical Imaging; Department of Bioengineering; School of Public Health; University of Arizona; Surgical Service and Radiology Service; Southern Arizona VA Health Care System; Arizona Alzheimer's Consortium.

Specific Aims:

Specific Aim 1: Determine the predictive values of plasma cytokine on SBIs.
Specific Aim 2: Determine the interaction between baseline cerebral blood flow and SBIs.

Background and Significance:

Reduced cerebral blood flow (CBF) is known to contribute to cognitive changes in patients with severe carotid disease[1,2]. Whereas hypoperfusion and embolism have been viewed as dichotomous etiologies, there is a growing appreciation that they interact in the concept of the hemodynamic risk zone[3,4], namely border zone region(s) of cortex that are vulnerable to decreased blood flow. Our distribution map of SBIs suggests that emboli tend to occur at a higher probability in these border zones[5]. We ***hypothesize*** that impaired washout is a mechanism that integrates hypoperfusion and embolization, and specifically poor clearance of emboli in regions of lower perfusion leads to increased incidence and size of microembolization. If the concept is proven correct, then there should be an overlap between the probability map of embolus deposition and localized cerebral perfusion asymmetries. Furthermore, the area defined by both brain maps, should they converge, will help to identify a group of patients at risk for procedure-related cognitive deterioration; and therefore, appropriate patient consultation and management can be individualized.

Increasing evidence supports the ability of the central nervous system to incite an inflammatory response to a variety of injuries including ischemia through a leaky blood-brain barrier[6]. Serum biomarkers are easily obtainable and can be adapted widely in various clinical settings as an indicator for clinically important outcomes. Unlike other clinical populations (e.g. stroke or AD) where injury-related biomarkers are difficult to obtain due to variability in the timing and etiology of injury, our patient cohort provides a unique opportunity as micro-injury occurs at a predictable time during interventions. We believe that systemic biomarkers correlated to SBIs can predict long-term cognitive changes following carotid intervention. The predictive value of serum biomarkers can be utilized to guide early cognitive rehabilitation for vulnerable patients. Early cognitive training and treatment in elderly adults has been shown to be effective in improving general cognitive function, memory, executive function, and everyday problem-solving ability[7,8].

This pilot project will leverage the resources from an ongoing VA funding and provide critical personnel support for more in-depth imaging and plasma analysis in collaboration with MRI Imaging Core. Our ***goal*** is to identify imaging and plasma biomarkers predictive of procedure-related SBIs and consequent cognitive impairment and dementia.

Preliminary Data, Experimental Design and Methods:

Through our previous NIH support, we evaluated 98 subjects who underwent carotid intervention. Plasma was obtained within 24 hours of intervention and analyzed for inflammatory cytokines using a Luminex magnetic bead-based assay. Despite an overall improvement in episodic memory at 1 month and 6 months postop compared to the preop baseline, 32% of the patients experienced significant memory decline (>10%) at 1 month and 36% at 6 months postop. After adjusting for key clinical variables, we revealed that interleukine (IL)-12p40 was an independent predictor for significant memory decline at 1-month postop. At 6 months, stromal cell-derived

factor 1-alpha (SDF1-α) and tumor necrosis factor-alpha (TNF-α) were independently associated with significant memory decline compared to the preop baseline[9].
We also evaluated the effects of procedure-related SBIs and volumes of SBIs on episodic memory changes following carotid intervention[10]. Volume is calculated by manually tracing procedure-related diffusing weight MRI (DWI)-lesions using MRIcron software. Episodic memory was measured using Rey Auditory Verbal Learning Test (RAVLT). A significant correlation was observed between infarct volume and changes in RAVLT long-delay recall and RAVLT short-delay recall at 1- and 6-month postop. Patients with an embolic volume >100mm^3 experienced procedure-related memory decline.

Methods:
For Aim 1, we will collect blood sample preop and within 24-48 hours postop. Plasma will be extracted and analyzed using commercially available ELISA assay or Western blot for individual cytokines. While exploring macrophage-related inflammatory cytokines, focusing on the cytokines identified in our previous report, as well as brain injury markers, NSE and S100B.
For Aim 2, procedure-related SBIs will be identified by new hyperintensities on postop DWI that are hypointense on corresponding ADC maps and not present on the preop DWI images. Each individual embolic infarct will then be manually traced using MRIcron neuroimaging software. The changes in plasma cytokine levels and postop plasma cytokines will be correlated with procedure-related SBIs.

Proposed One-Year and Long-Term Outcomes:
We expect to generate useful preliminary information on the relationship between baseline CBF, procedure-related SBIs, and plasma biomarkers at one year. These preliminary data are critical for applying to our larger cohort and a new NIH grant application in next 24 months.

Year End Progress Summary:
Utilizing the data collected from the pilot project and the data from the previous funding period, we evaluated the potential predictive values of plasma cytokine on procedural-related MRI-evident silence brain infarct (SBIs). Transfemoral stenting procedures are associated more SBIs and, therefore, we focused on analysis on this cohort of patients. The table depicted the relationship between procedure-related silent brain infarcts and cytokine levels following carotid stenting (N=77).

In addition, we analyzed how diabetes affect brain volume and cognitive function in patients with severe carotid disease. High resolution T1 images were processed using longitudinal FreeSurfer pipeline. We observed significant brain structural effects of diabetes, specifically, diabetes shows regionally selective reductions in cortical thickness/volume, and these effects remain statistically robust after adjusting for key vascular and metabolic risk factors. This indicates that diabetes contributes unique variance to neuroanatomical vulnerability beyond the broader cardiometabolic milieu. In addition, we evaluated cognitive relevance of affected regions. We demonstrated that the regions showing diabetes-related structural compromise are also those whose integrity predicts cognitive performance, particularly in executive function and processing speed, and within temporal cortices, episodic memory. These associations persist after adjusting for diabetes

status, demonstrating that the affected tissue is cognitively eloquent. The findings suggest that diabetes preferentially affects brain regions with high cognitive relevance, even in the absence of detectable group-level cognitive impairment. This pattern is consistent with the idea that structural MRI may detect early or subtle neural vulnerability before overt behavioral decline becomes measurable.

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ARIZONA ALZHEIMER'S CONSORTIUM
update2025-2026 Scientific Progress Report

Novel Synaptic Signaling Mechanisms as Alzheimer's Disease Therapeutic Targets.
Ayanabha Chakraborti, PhD, James A. Bibb, PhD. Department of Translational Neurosciences, University of Arizona College of Medicine – Phoenix; Arizona Alzheimer's Consortium.

Specific Aims:

Aim 1: Characterize the role of synaptic Cdk5 and Dyrk1A signaling in regulating cognitive function in normal and AD model mice. We hypothesize that Cdk5 and Dyrk1A orchestrate distinct, activity-dependent synaptic protein networks in the hippocampus that are essential for associative learning, and that dysregulation of this kinase-specific interactome network contributes to cognitive deficits in AD. To test this, we will define the synaptic interactomes of Cdk5 and Dyrk1A in the hippocampus in wild-type (WT) and AD model mice.

Aim 2: Evaluate the effects of novel Cdk5 and Dyrk1A targeted therapeutics for pro-cognitive effects in normal and AD model mice. We hypothesize that pharmacological inhibition of Cdk5 or Dyrk1A will mitigate hippocampal-dependent cognitive alterations and reverse AD-related disruptions in synaptic function. To test this, we will administer novel selective Cdk5 and Dyrk1A inhibitors to wild-type and AD model mice and assess their effects on hippocampal-dependent cognition and synaptic signaling.

Background and Significance:

Synaptic dysfunction is an early and central feature of Alzheimer's disease (AD) and is closely tied to cognitive decline. The proline-directed kinases Cdk5 and Dyrk1A regulate synaptic plasticity under physiological conditions but become dysregulated in AD, contributing to tau hyperphosphorylation, impaired NMDA receptor signaling, and synaptic failure. We have shown that Cdk5 phosphorylates the NR2B subunit at Ser1116 to regulate its synaptic trafficking, a mechanism central to long-term potentiation and memory. Despite this progress, the activity-dependent synaptic interactomes of Cdk5 and Dyrk1A during learning, and how they are disrupted in AD, remain undefined. This project applies in vivo proximity labeling (TurboID) to map these kinase-specific synaptic interactomes and evaluates the pro-cognitive efficacy of two novel, brain-penetrant inhibitors, 25-106 (Cdk5) and Leucettinib-21 (Dyrk1A), in wild-type and 5xFAD mice. Defining these kinase-specific interactomes will identify novel targets for early cognitive intervention in AD, directly addressing the field's urgent need for disease-modifying therapeutics.

Preliminary Data, Experimental Design and Methods:

Our prior studies have shown that Cdk5 functions as a key regulator of synaptic plasticity and cognitive function through phosphorylation of synaptic proteins critical for plasticity and memory. Specifically, Cdk5 phosphorylates Ser1116 of the NR2B subunit of the NMDA receptor, preventing its surface expression, as a basal state for naïve synapses. We also identified 25-106 as a selective, brain-permeable systemic Cdk5 inhibitor with favorable pharmacokinetics and neuroprotective efficacy. In this project, for the first time, we will assess the pro-cognitive and therapeutic potential of this compound in the context of AD.

We will combine molecular, behavioral, and pharmacological approaches to examine how Cdk5 and Dyrk1A regulate normal synaptic function and contribute to synaptic dysregulation in AD. Our strategy consists of two integrated components: (1) proximity-dependent biotinylation using TurboID to map the activity-dependent synaptic interactomes of Cdk5 and Dyrk1A in male and female wild-type (WT) and 5xFAD mice during learning, and (2) pharmacological assessment of

the pro-cognitive efficacy of selective kinase inhibitors, 25-106 and Leucettinib-21, through touchscreen-based behavioral testing and synaptic protein analysis.

Proposed One-Year and Long-Term Outcomes:

The data generated from this project will serve as a foundation for a collaborative, multi-PI NIH R01 grant application focused on kinase-mediated synaptic dysfunction and therapeutic targeting in AD. In parallel, we are engaged in library screening for novel Cdk5 inhibitors with improved pharmacokinetic, toxicity, selectivity, and efficacy profiles to advance toward pre-clinical testing. The interactomics data will reveal new therapeutic targets, while positive outcomes with Leucettinib-21 could support extension into clinical trials.

Year End Progress Summary:

We designed and generated three AAV9 constructs for *in vivo* proximity-labeling studies: a Cdk5r1 (p35)-TurboID-V5-P2A-EGFP construct, a Dyrk1A-TurboID-V5-P2A-EGFP construct, and a TurboID-V5-P2A-EGFP control construct, each under the control of the neuron-specific SYN1 promoter. The corresponding plasmid constructs were first validated *in vitro* by transient transfection into HT22 cells, an immortalized mouse hippocampal neuronal cell line. Following transfection, cells were supplemented with biotin to enable TurboID-mediated proximity biotinylation. Fluorescence imaging confirmed successful transfection and EGFP expression in HT22 cells. Western blotting with an anti-V5 antibody confirmed expression of the p35-TurboID and Dyrk1A-TurboID fusion proteins at their expected molecular weights. In addition, streptavidin-based blotting of cell lysates following biotin supplementation demonstrated robust protein biotinylation in cells expressing the TurboID-containing constructs. Together, these findings confirmed appropriate expression of the p35-TurboID and Dyrk1A-TurboID fusion proteins and demonstrated their capacity to mediate robust protein biotinylation *in vitro*, supporting their subsequent use *in vivo*. We next performed stereotaxic hippocampal injections of the AAV9-p35-TurboID, AAV9-Dyrk1A-TurboID, and AAV9-TurboID control viruses in mice. The injected animals are currently completing the post-injection interval required for adequate viral expression. Following this interval, biotin will be administered, and hippocampal tissue will be collected for synaptoneurosome preparation. Biotinylated proteins will then be isolated by streptavidin affinity enrichment and analyzed by LC-MS/MS to characterize the p35- and Dyrk1A-associated protein networks.In parallel, we optimized the touchscreen-based paired-associate learning (PAL) task as a hippocampus-dependent cognitive assay for evaluating learning-associated interactome remodeling and the effects of pharmacological intervention. The PAL testing protocol was standardized through optimization of key procedural steps, including stimulus presentation and training criteria, to support reproducible assessment of associative memory performance. The assay is now ready for use in the wild-type and 5xFAD inhibitor-treatment cohorts.

The principal challenge during this reporting period was the time required to establish the 5XFAD breeding colony and generate sufficient numbers of appropriately aged animals for behavioral studies. Cohort generation has progressed more slowly than initially anticipated. Breeding and colony-management strategies have therefore been adjusted to increase cohort sizes and improve the consistent availability of age-matched 5XFAD mice. As the 5XFAD cohorts reach the required ages, we will complete the inhibitor-dosing studies with 25-106 and Leucettinib-21 and evaluate their pro-cognitive effects using touchscreen-based behavioral testing. With the viral constructs validated, the injected animals progressing toward tissue collection, and the behavioral assay optimized, the remaining experimental work is positioned for completion within a short period of time.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Characterizing Somatic Mosaicism in Alzheimer's Disease Brains. Isabelle Schrauwen, PhD, Geidy Serrano, PhD, Ileana Lorenzini, PhD, Thomas Beach, MD, PhD. Translational Neuroscience, University of Arizona - College of Medicine, Phoenix; Brain & Body Donation Program, Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

This project aims to comprehensively investigate somatic variants in the brain tissues of individuals with Alzheimer's disease (AD) by utilizing deep sequencing techniques. The focus of this study will be on identifying high-impact, rare somatic mosaic variants with potential deleterious effects, which are rare in population databases and neurotypical control brains. To distinguish somatic mosaic variants from germline variants, we will compare DNA sequence data from brain tissue with matched DNA derived from another non-brain tissue ("germline control"). The goals are to determine how frequently predicted deleterious somatic variants occurs in Alzheimer's disease brains, uncover novel risk genes and disease mechanisms, and ultimately inform the development of targeted therapies.

Background and Significance:

While genome-wide association studies (GWAS) and family-based studies have identified numerous germline variants associated with Alzheimer's disease (AD), their discovery potential may be approaching saturation. Somatic mosaic variants, which arise post-zygotically and may be restricted to specific cell types or brain regions, represent an underexplored source of genetic variation that could contribute to AD pathogenesis. These rare, high-impact variants may influence mechanisms such as tau pathology and neuroinflammation that are not captured by germline studies. However, due to technological and resource limitations, somatic mosaicism has rarely been investigated systematically at the exome or genome-wide scale in AD. A comprehensive genome-wide approach has the potential to uncover novel disease mechanisms, biomarkers, and therapeutic targets.

Preliminary Data, Experimental Design and Methods:

Preliminary Data: Although somatic mosaicism remains understudied in Alzheimer's disease (AD), emerging evidence supports its role in neurodegeneration. Our team has extensive expertise in detecting somatic variants in brain disorders using high-depth sequencing and structural variant analyses, providing a strong foundation for this work. We will leverage the Arizona Brain & Body Donation Program, which includes 985 well-characterized AD brain specimens.

Experimental Design and Methods: We will perform high-depth exome sequencing of matched brain and a control tissue DNA from 40 AD cases to identify somatic single nucleotide, insertion/deletion, and structural variants. Somatic variants will be distinguished from germline variants using established bioinformatic pipelines, rigorously filtered, annotated, prioritized based on predicted pathogenicity and AD relevance, and validated where appropriate. Candidate variants will be compared with neurotypical controls, with follow-up functional studies (e.g., single-nucleus sequencing or spatial transcriptomics) performed for high-priority findings.

Proposed One-Year and Long-Term Outcomes:

Findings from this study will inform a larger-scale investigation in both cases and controls. We expect to use the preliminary results from this project to submit an NIH or other appropriate funding agency in 2026.

Year End Progress Summary:

We obtained prefrontal cortex samples and kidney (as the germline control) from 40 AD cases and 40 neurotypical controls to identify somatic single nucleotide, insertion/deletion, and structural variants. DNA was extracted and exome sequencing was performed on both the prefrontal cortex and germline control DNAs. Due to delays in finalizing the material transfer agreement, tissue acquisition occurred later than anticipated. However, bioinformatic processing of the resulting data is currently underway and is expected to be completed within a short timeline. Somatic variants will be distinguished from germline variants and prioritized based on predicted pathogenicity and AD relevance. We will follow-up functional studies (e.g., single-nucleus sequencing or spatial transcriptomics) performed for high-priority findings.

ARIZONA ALZHEIMER'S CONSORTIUM
2025-2026 Scientific Progress Report

Hearing Loss Mechanisms and Alzheimer's Disease. Ebenezer N. Yamoah, PhD. University of Arizona-College of Medicine, Phoenix; Arizona Alzheimer's Consortium.

Specific Aims:

We hypothesized that the BLB is characterized by increased permeability in AD, distinct from that in normal aging, and that this increase is associated with elevated Aβ levels in the CD. Tau and Aβ proteins mediate TJ weakening in the StV and the sensory epithelia of the CD, resulting in K^+ leakage from the endolymph (~140 mM) to the perilymph (~1 mM), triggering membrane depolarization, Ca^{2+} overload, synaptopathy, and neuronal death. The **Specific Aims are:**

Aim 1: Identify the behavior, mechanisms, and significance of altered BLB in AD models. Hypothesis: We hypothesize that AD-mediated changes in the BLB result in increased τ Aβ proteins in the CD. Weakened TJs are caused by a decline in the expression of TJ proteins (TJP), claudin-9 (*Cldn9*), and occludin (*Ocln*). Experiments: We will test our hypothesis using biochemical and image analyses in AD mouse models.

Aim 2: Test *in vivo and in vitro* alterations of synaptic functions resulting from exposure to AD-biomarkers and synaptic depolarization mediated by increased perilymph K^+. Hypothesis: We hypothesize that prolonged exposure to AD biomarkers and membrane depolarization results in synaptic structure and function changes. Experiments: Alterations in synaptic structure and functions will be tested in AD models. Thus, integrative mechanistic insights into HL's etiology as a potential precursor to AD will be elucidated, and potential therapeutic strategies will be proposed.

Background and Significance:

The prevailing paradigm demonstrates that the diagnosis of HL is a risk for developing AD and dementia. however, the mechanistic links remain unknown. Since progressive HL is a hallmark of aging, AD-related HL is often masked and considered an independent disease. Since HL often precedes robust cognitive impairment in AD, insights into the mechanistic links would enhance early detection, intervention, and potential treatment of the disease. We will present mechanistic evidence demonstrating that the CD may serve as a hub for early AD detection and therapeutic intervention. Our findings' significance transcends HL's molecular mechanisms in AD and shifts the paradigm to possible clinical and translational interventions.

(b) Scientific Premise

We demonstrate that AD mouse models (amyloid precursor protein/presenilin-1 double-transgenic B6.Cg-Tg(APPswe,PSEN1dE9)85Dbo/Mmjax (APP/PS1.APP/PS1; ADCg), B6.Cg-Tg(APPSwFlLon, PSEN1*M146L*L286V)6799Vas/Mmjax (5XFAD), and VB-Tg(tetO-MAPT *P301L) #Kha/JlwsJ (MAPT) mice), show microangiopathy of the BLB. These transgenic lines have potential limitations of random insertion and overexpression that may produce off-target effects that may not represent the authentic human diseased conditions. We have used the transgenic lines as proof-of-principle in the preliminary data and, motivated by the results, have generated knock-in (ki) mouse models of the human mutations (see attached letter Cyagen/Taconic). After ongoing backcrossing from C57/B6 to CBA-CaJ mouse lines, the three ki models will test the hypotheses.

We hypothesize that τ, Aβ, and other blood-borne substances in the StV and the cochlear endolymph alter TJ integrity of the sensory epithelium. Because the cochlear endolymphatic volume (humans, ~8 μl, mouse ~0.2 μl; is >100-fold smaller than the CSF space (humans, ~150 ml, mice, ~36 μl), concentrations of blood-borne substances in the endolymph would be higher than in the CSF.

Early studies identified hair cells (HC) and spiral ganglion neurons (SGN) as loss from human temporal bones in AD patients. Subsequent analyses focused on the detection of characteristic plaques and tangles in the auditory cortex, and synaptopathy in central neurons of the auditory pathway. However, recent studies using the AD mouse model, 5XFAD, demonstrated reduced acoustic startle response and HC loss as early as 3-4-months old before olfactory and cognitive dysfunction. The implications and limitations of these findings are several-fold. 1) HL may be added to one of the sensory prodromes for AD. 2) Cognitive tests for AD that rely on auditory stimuli should be re-evaluated. 3) Finally, the findings are masked with caveats, in that the background of the transgenic mice used in the recent studies has accelerated ARHL, making it challenging to segregate ARHL and AD-related HL. We backcrossed the three AD mouse models onto CBA-CaJ mouse and the knock-in lines.

Preliminary Data, Experimental Design and Methods:

(c) Approach

All AD transgenic models have been backcrossed (12 generations) onto CBA-CaJ background mice ki lines.APP/PS1.APP/PS1 (ADCg), 5XFAD, and MAPT mouse models have an increased hearing threshold. To test our hypothesis, we performed auditory brainstem recordings (ABR) in three AD mouse models at 50-weeks compared to age-matched CBA-CaJ control mice. We illustrate data from 5XFAD mice relative to their controls and have summarized the corresponding data for APP/PS1.APP/PS1 and MAPT mice. 5XFAD mice exhibit early-onset HL, but their age-matched controls have no apparent HL. The findings that APP/PS1, 5XFAD, and MAPT mice show HL compared to their controls are consistent with our central hypothesis. (**Figs. 1).**

Age-related changes in learning and memory, olfactory, and hearing test We used force alteration in Y-maze, novel object recognition, and passive avoidance conditioning as measures of learning and memory and olfactory behavior test. For a pilot study, we compared data from two age groups, 12- and 24-week-old 5XFAD mice.

Enlargement of BM of the BLB in StV capillary and TJs in APP/PS1.APP/PS1, 5XFAD, and MAPT mice. We used transmission electron microscopy (TEM), to assess the ultrastructure of the BLB of the three AD mouse models, focusing on the StV capillary bed.

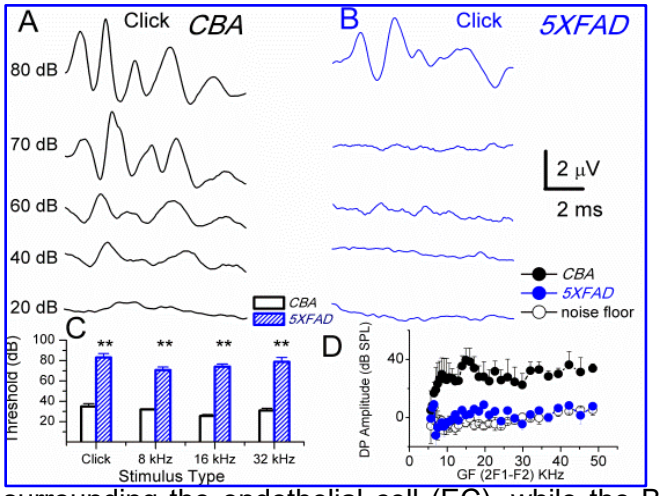


Fig. 1. Increased ABR thresholds in AD mouse models. A & B. Representative ABR waveforms from CBA control mice compared to age-matched 5XFAD (50 weeks old). **C**. Threshold for 5XFAD (**n**=13) and their age-matched CBA (**n**=13) mice (***p*<0.01). Similar sound threshold (in dB SPL) data was collected for APP/PS1.APP/PS1 at 50 weeks for clicks 8, 16, and 32 kHz were 33±4, 32±5, 32±3, and 31±4; APP/PS1.APP/PS1; 80±5, 78±6, 75±5, and 76±4, respectively (n=10; ***p*< 0.01). For the MAPT mice, control thresholds at 50 weeks for clicks 8, 16, and 32 kHz were 30±5, 22±3, 30±5, and 26±6; and MAPT were 65±5, 62±5, 65±7, and 65±8, respectively (n=10; **p<0.01). **D.** Distortion product (DP)grams for CBA and 5XFAD mice at 50 weeks. The distortion product otoacoustic emission (DPOAE) levels for the 5XFAD mice were distinguishable from the control and background (noise floor, NF; n=10). Similar data were obtained for APP/PS1.APP/PS1 and MAPT mouse lines.

A cross-section of a StV capillary from CBA mouse (12 weeks old) shows a thin BM surrounding the endothelial cell (EC), while the BM around the pericyte (PC) is slightly wider. Three independent histologists, “blind” to the experimental groups, measured control mean BM thickness of 54±6 nm (n = 606 from 5 animals). StV capillary BM in age-matched APP/PS1.APP/PS1 and 5XFAD were nearly doubled in thickness, averaging (in nm) 120±7 and 118±10, respectively (n = 411 from 4 animals in each strain; $p<0.01$. The PC's cytoplasm in the AD mouse models was often less dense, indicating fewer intracellular organelles. The BM

thickness in the MAPT mice was also increased (101±9 nm, n = 65 from 3 animals; $p<0.01$). Because the changes in the BM of the BLB in the StV dovetailed nicely with the reported alteration in the BBB and BCSFB, we predicted that increased permeability of the BLB would ensue, leading to altered StV TJ integrity.

We analyzed TJ-width between HC-Deiter cells (DC) and HC-phalangeal cells of APP/PS1.APP/PS1 mouse cochlea compared to control mice. The TJs' apical aspects in the AD mouse models were compromised with swollen pockets and increased width (**Fig. 1**). The TJ components in the inner ear are outlined. Different isoforms of claudins are expressed differentially in CD cells, underscored by HL associated with mutations of *Cldn9* and[61] *Cldn11*.[110] To determine the mechanisms for the altered TJ morphology in AD sensory epithelium, showing retraction of the apical portions, we have identified two TJ proteins (TJP), Cldn9 and Ocln, which are significantly down-regulated at the protein level (**Fig. 2**).

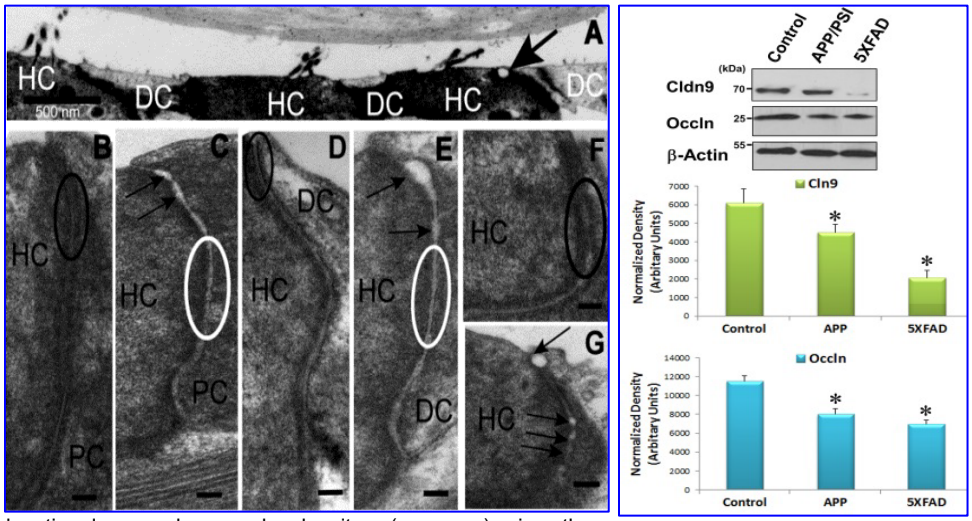


Fig. 2 (Left). Outer hair cell (OHC) junctional complexes. A. A low magnification view shows the three OHCs interspaced with DC's phalangeal processes in a 5XFAD mouse. An enlargement in the intercellular junctional space (black arrow) is visible very near the apical end of the tight-adherens junction between OHC3 (third row) and the DC3 phalangeal process (DC). Representative OHC junctional complexes from control mice **(B, D,** and **F)** have a fairly uniform width along the length of the intermembrane junctional junctional complex and density (grayness) in the proteins. Increased density of the cytosolic network adjacent to the junctional complex (black ovals) can be detected on the HC side of the junction in **B** and both the HC and DC phalangeal processes in **D** and **F**. These are characteristic of tight and adherens junctions, as well as desmosomes. The dark gray to black regions (black ovals) most likely represents actin and junctional proteins' cytoplasmic aspects. In contrast, the junctional complexes of 5XFAD mice **(C, E,** and **G)** showed less density in the cytoplasmic protein network (white ovals) immediately adjacent to the basolateral cell edge (**E** and **G** black ovals) and a decrease in the density (grayness) of the intercellular junctional proteins. Increased intercellular width (black arrows) was evident at multiple areas of the junctional length in all 5XFAD samples (black arrows), which mimics the loss of cadherin proteins in models of dysfunctional epithelial cell junctions. The mean TJ width for control was 13.2±2.1, and 5XFAD was 17.5±3.8 (n=99, $p<0.05$). OHC= outer hair cell; DC= Deiters cells phalangeal process; TM= tectorial membrane; PC= outer pillar cell; black star: tight junction; white star: adherent junction; white arrows: desmosome; Scale bar in **B-G** = 100 nm.

(Right panel). Reduced expression of TJ proteins in AD models' cochlear sensory epithelia compared to controls (CT). A. Cochlear ducts of at least 20 CBA mice (~24 weeks old) were isolated. The sensory epithelia were carefully dissected. Changes in expression of Cldn9 and Ocln were determined compared to aged-match APP/PS1 APP/PS1 and 5XFAD mice. Cldn9 and Ocln levels were reduced in the AD model sensory epithelia. All comparisons were made using loading controls. □-Actin was used as a control. Quantitative RT-PCR (qRT-PCR) using the same mouse models as in **A** shows a similar decline in AD models at the transcript levels of *Cldn9* and *Ocln*. GAPDH was used as a control for the qRT-PCR data.

Proposed One-Year and Long-Term Outcomes:

The long-term outcome is to generate pilot data nimal models for a competitive R01 application. We anticipate submitting a national application early 2027, February 5th deadline.

Year End Progress Summary:

Should be 1-2 pages detailing progress made from 07/01/23 to 06/30/24. Explain progress made towards the proposed one-year outcomes. Describe findings and provide explanation for any challenges encountered. Describe progress made on the proposed long-term outcomes. Include future grant applications, publications and collaborations that arose from the research.

During the past year, we focused on structural studies of axon terminals in the cochlear nucleus (CN), inferior colliculus (IC), and superior olivary complex (SOC), comparing young and old mice, as a prelude to studying AD mouse models. We used electron microscope tomography to generate high-resolution volumes.

The Mitochondrial Complexity Index (MCI) was lowered for Old SOC Terminals, But Not for Old CN or IC Terminals.

The MCI provides a quantitative measure of the shape of mitochondria, independent of mitochondrial volume. A spherical mitochondrion will have an MCI of 1. The more elongated a mitochondrion is, the higher the MCI. Additionally, branched mitochondria will have a higher mitochondrial capacity index (MCI). Branching was rarely observed in the presynaptic terminals of SOC, IC, or CN, so the increase in MCI was due almost exclusively to elongation. We found that the MCI was smaller, resulting in more rounded mitochondria, for the 18-24 month SOC terminals compared with the 3-month terminals, but not for the IC or CN terminals. This rounding may have been produced from increased mitochondrial fission or decreased fusion in the aged terminals.

The Mitochondrial Crista Density Was Lower for Old SOC, IC, and CN Terminals.

The mitochondrial cristae density is strongly correlated with the capacity of mitochondria to produce ATP. Because we found a lowered crista density in aged outer hair cell mitochondria (Perkins et al., 2020), we investigated the crista density of young and old terminals in the SOC, IC, and CN. The cristae density is defined as the total cristae membrane surface area divided by the mitochondrial volume and has units of micrometers per micrometer. As with the OHC mitochondria, we found a decrease in mitochondrial cristae density in the 18-24-month presynaptic terminals impinging on primary neuronal somata or proximal dendrites compared with the 3-month presynaptic terminals in the SOC, IC, and CN. This lowered crista density suggests a reduced capacity of aged excitatory terminal mitochondria to produce ATP. To our knowledge, this is the first report of reduced crista density in aged brain mitochondria.

Autosegmentation of the SVs in SOC, IC, and CN Terminals.

Because there are typically several hundred synaptic vesicles (SVs) in each presynaptic terminal of the SOC, IC, or CN, their manual segmentation would be very time-consuming. This past year, we have made good progress using a machine-learning algorithm, called CDeep3M, for the autosegmentation of SVs in EM tomography volumes. The first step was to generate a training volume of manually segmented SVs in one terminal. Ground-truth segmentation was generated using the sculpt option in the IMOD Drawing Tools menu. A 300 x 300-pixel sub-volume was used for initial training. Predicted contours in three 2000 x 2000-pixel generated models were then manually corrected and used for re-training. Ground truth segmentations were prepared for an additional 2000 x 2000-pixel volume to validate prediction accuracy. A uniform manual threshold was applied in FIJI to the prediction output to separate joined SV contours, and adjustments were made as needed to incomplete SV contours in the resulting model to retain fidelity to ground-truth segmentations. Before analyzing the segmented vesicle dimensions and morphologies, two methods of thresholding were employed to exclude outliers and biologically irrelevant surfaces. In the first method, only vesicles defined by a diameter of 24-70 nm in the Z-dimension were considered for analysis, as this range corresponds to the known sizes of SVs and templates used in prior studies. Via the second method, SVs with contour numbers considered statistical outliers ($|z\text{-score}| \geq 3$) were excluded from the analysis. The autosegmentation achieves greater than 95% accuracy, but further work is needed to address some false positives, such as structures associated with the plasma membrane or mitochondrial cristae. One possible solution is to try autosegmentation of mitochondria to mask them, thus excluding that portion of the volume that contains a few false positives.



2025 – 2026

Publications & Manuscripts

2025 Publications and Manuscripts

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2025 – 2026

Current & Pending Grants

2025-2026 Current Grants

Steven Rapcsak (Site PI) 09/01/2021 - 06/30/2026
NIH/NIA via Arizona State University $911,967
P30AG072980 (Langbaum)
Arizona Alzheimer's Disease Research Center

Steven Rapcsak (Co-I) 08/15/2022 - 04/30/2027
NIH via University of Arizona $46,485
R01AG068098 (Grilli)
Tracking autobiographical thoughts: a smartphone-based approach to identifying cognitive correlates of Alzheimer's disease biomarkers and risk factors

Steven Rapcsak (Co-I) 12/01/2022 - 06/30/2026
NIH via University of Arizona $83,318
R01EB032674 (Saranathan)
Next-Generation thalamic nuclei visualization and segmentation methods

Emily Edmonds (Project PI) 09/01/2023 - 08/31/2028
NIH via University of California, San Diego $138,259
RF1AG082726 Heterogeneity of subtle cognitive decline phenotypes in community-dwelling older adults

Emily Edmonds (Project PI) 07/01/2025 - 06/30/2026
Arizona DHS via Arizona Alzheimer's Consortium $68,400
Clinical profiles and predictors of cognitive performance in plasma p-tau217 positive individuals in memory clinic and research settings

Steven Rapcsak (Project PI) 07/01/2025 - 06/30/2026
Arizona DHS via Arizona Alzheimer's Consortium $68,400
Partnering with primary care for clinical implementation of blood-based biomarkers to facilitate early detection and access to disease-modifying treatments for Alzheimer's disease

Emily Edmonds (Co-I) and Steven Rapcsak (Co-I) 09/30/2025 - 09/29/2030
NIH/NIA via University of Arizona (Grilli) $874,926
RF1AG093527 Optimizing semantic memory measures of Alzheimer's disease biomarkers

Emily Edmonds (MPI) and Steven Rapcsak (MPI) 07/01/2026 - 06/30/2027
Arizona DHS via Arizona Alzheimer's Consortium $152,000
Concordance between biological and clinical diagnosis/staging of Alzheimer's disease in research, memory clinic, and primary care cohorts

Robert Bowser (Co-I) 12/01/2021 - 11/30/2026
R61 NS119642-02 $3,830,563
NIH/NINDS
Targeting CNS expression of chitinases as a novel therapy for ALS

Robert Bowser (Co-PI) 08/01/2022 - 07/31/2027
R01 NS091299-06 $3,200,000
NIH/NINDS

Translation dysfunction in neurodegeneration

Anna Burke (PI)	05/2026 - 04/2031
RFGA2026-006-001	$5,000,000
Arizona Biomedical Research Centre (ABRC)	
A Phase 1/2 Trial of Magnesium-Ibogaine for PTSD and TBI: Safety, Efficacy, and Biomarkers of Response	

Anna Burke (Sub-I)	08/15/2021 - 07/31/2027
7R01AG073212 (Sabbagh/Decourt/Wilson)	$2,500,00.00
Repurposing Siponimod for Alzheimer's Disease	

Anna Burke (Sub-I)	04/01/2022 - 03/31/2027
Alzheimer’s Drug Discovery Foundation (ADDF)	$1,396,475
MCLENA-2: Assessment of Lenalidomide for Alzheimer’s Disease	

Anna Burke (Sub-I)	09/15/19 - 08/31/25
TRC-DS 1R61AG066543-01 (R61AG066543)	$306,000 to date
Alzheimer's Clinical Trial Consortium for Down Syndrome (ACTC-DS) Trial-Ready Cohort - Down Syndrome (TRC-DS)	

Anna Burke (Sub-I)	01/01/22 - 06/30/26
ADRC- 1P30AG072980-01	$530,221.50
Arizona Alzheimer’s Disease Research Center	

Anna Burke (Sub-I)	09/15/22 - 07/31/27
ADNI-U19AG024904	not to exceed $1,200,000
Alzheimer's Disease neuroimaging initiative -4	

Jordan Killion (PI)	07/01/2025 - 06/30/2026
BNF 455003034424	$111,333
Traffic Related Air Pollution and Tree Density on Risk of Alzheimer’s Disease	

Jordan Killion (Sub-I)	01/01/2023 - 12/31/2026
GR-ARPA-BNF-050123-01	$9,994,276
Impact and mechanisms of COVID on neurological function and health outcomes	

Brittany Krzyzanowski (PI)	07/01/2025 - 06/30/2026
BNF 455003034424	$111,333
Traffic Related Air Pollution and Tree Density on Risk of Alzheimer’s Disease	

David Medina (PI)	07/01/2025 - 06/30/2026
BNF	$111,333
Exploring RNA m6A Modifications: Pathways and Impacts in Dementias	

David Medina (PI)	07/01/2023 - 06/30/2026
DOD AL2201013	$782,284
Retinoid-activity gene therapy for the treatment of amyotrophic lateral sclerosis	

Sylvia Perez (PI) 04/01/2026 - 03/31/2028
R01 AG081286-2 (Perez/Mufson) $1,458,662
NIH/NIA
Default mode network dysfunction in Down syndrome

Sylvia Perez (Co-I) 1997-2027
P01AG014449 (Mufson PI)
NIH/NIA
Neurobiology of mild cognitive impairment in the elderly

Sylvia Perez (PI) 07/01/2026 - 06/30/2027
Arizona Alzheimer's Consortium (Perez/Verpeut) $111,333
AAC/BNF
Cerebellar perineuronal net dysfunction in prodromal Alzheimer's disease

Susan Racette (MPI) 09/30/2021-01/31/2027
R01 AG071717 (Das/Racette/Redman) $7,838,485
NIH/NIA
Legacy Effects of CALERIE, a 2-year Calorie Restriction Intervention, on Hallmarks of Healthspan and Aging

Susan Racette (Co-I) 02/15/2021-01/31/2030
R33 AG070455 (Huffman) $2,472,781
NIH/NIA
Enhancing the CALERIE Network to Advance Aging Biology 2.0

Susan Racette (Co-I) 08/01/2022-07/31/2027
R61 HL155858 (Peterson) $2,438,542
NIH/NHLBI
The Inorganic Nitrate and eXercise performance in Heart Failure (iNIX-HF): - a phase II clinical trial

Susan Racette (Co-I) 12/01/2024-11/30/2027
ABA (Kavouras) $2,213,993
American Beverage Association
Adequate Hydration and Health Outcomes

Susan Racette (MPI) 05/01/2023-12/31/2026
BNF (Geda/Racette) $400,000
Barrow Neurological Foundation
Time-Restricted Eating in Alzheimer's Disease: The TREAD Trial

Susan Racette (MPI) 07/01/2025-06/30/2026
AAC (Sabbagh/Racette) $111,333
Arizona Alzheimer's Consortium and Barrow Neurological Foundation
Acute Effects of Exercise, With and Without Anti-Amyloid Therapy, on Fluid Biomarkers in Patients with Mild Cognitive Impairment

Marwan Sabbagh (Sub I) 01/2023 - 12/2026
GR-ARPA-BNF-050123-01 $9,994,276

Department of the Treasury
Impact and mechanisms of COVID on neurological function and health outcomes

Marwan Sabbagh (MPI) 01/01/2023 - 12/31/2027
GC-2013717 (Sabbagh/Decourt/Wilson) $1,396,475
Alzheimer's Drug Discovery Foundation (ADDF)
Repurposing lenalidomide for early Alzheimer's treatment

Marwan Sabbagh (MPI) 08/15/2021 - 07/31/2027
7R01AG073212 (Sabbagh/Decourt/Wilson) $2,500,00
NIH/NIA
Repurposing Siponimod for Alzheimer's Disease

Marwan Sabbagh (PI) 01/01/2023 - 9/30/2026
GR-ARPA-BNF-010123-03 (Sabbagh) $3,142,468
Office of the Governor of the State of Arizona (GVA);
American Rescue Plan Act (ARPA)
Project 2: Impact and mechanisms of COVID-19 on neurological function and health outcomes

Marwan Sabbagh (MPI) 07/01/2025 - 06/30/2026
25-500-289-30-53 (Sabbagh/Racette) $111,333
AAC and BNF
Acute Effects of Exercise, With and Without Anti-Amyloid Therapy, on Fluid Biomarkers in Patients with Mild Cognitive Impairment

Marwan Sabbagh (Site PI) 04/01/2022 - 06/30/2026
1P30AG072980 (Reiman) $560,436
NIH/NIA
Arizona Alzheimer's Disease Research Center

Marwan Sabbagh (PI) 07/01/2022 - 06/30/2026
2-500-046-30-03 (Sabbagh) $230,000
AAC and BNF
Hispanic Enrollment in Alzheimer's Research Trials (HEART)

Rita Sattler (MPI) 07/01/25-08/31/27
NIH/NINDS R21 NS141011-01 $433,795
Cross validation of gene expression changes in C9orf72 FTD using Drosophila and human model systems.

Rita Sattler (PI) 07/01/24-06/30/26
Target ALS Consortium $1,000,000
Mechanisms of glial-associated TDP-43 pathology and contributions to neurodegeneration

Rita Sattler (PI) 05/01/26-04/30/27
Robert Packard Center for ALS Research $80,000
Mechanisms of glial-associated TDP-43 pathology and contributions to neurodegeneration

Rita Sattler (PI) 04/11/24-08/31/27
NIH/NINDS 3R01NS120331-03S1 $155,884
(Diversity Supplement award)

The role of an aberrant synaptome in microglia-associated synaptic pruning in C9orf72 FTD.
Rita Sattler (PI) 04/01/24-03/31/27
Department of Defense AL230149 $772,545
The role of TDP-43 associated cryptic exon inclusion in KALRN on C9orf72-mediated cortical neurodegeneration.

Rita Sattler (PI) 09/01/23-08/31/27
Muscular Dystrophy Association #1063968 $300,000
Role of astrocyte-microglia crosstalk in C9orf72-mediated cortical neurodegeneration.

Rita Sattler (Co-PI) 09/01/23-08/31/28
NIH/NINDS R01 NS091299-06A1 $3,215,000
RNA dysregulation in neurodegeneration.

Rita Sattler (Multi-PI) 05/01/23-12/31/26
State of Arizona, GR-ARPA-BNF-050123-01 $10,000,000
Impact and mechanisms of COVIID on neurological function and health outcomes

Rita Sattler (PI) 09/01/21-08/31/27
NIH/NINDS R01 NS120331-01A1 $4,073,311
Microglia contribution to disease pathogenesis in C9orf72 ALS/FTD

Leslie Baxter (PI) 12/07/2023-11/30/2028
R01 MH132746-02 (Braden) $160,932
National Institute of Mental Health
The Aging Autistic Brain: Multi-modal imaging to predict accelerated memory decline

Leslie Baxter (PI) 07/01/2023-06/30/2027
FP00145447 $68,968
State of Arizona
Supporting Autistic Adults of All Ages: A Phase 2 Randomized Controlled Trial of the Strengthening Skills Program (SSP) to Improve Functional Independence, Quality of Life, and Employment Outcomes

Richard Caselli (Co-I) 07/2021-06/2027
ADHS14-052688 (Woodruff) $3,724,000
Arizona Department of Health Services
Normal and Pathological Aging (Preclinical Alzheimer's Disease)

Richard Caselli (Co-I) 09/30/2020-03/31/2026
R01 AG069453-05 (Reiman) $1,127,104
National Institute on Aging
APOE in the Predisposition to, Protection from and Prevention of Alzheimer's Disease

Shannon Chiu (PI) 01/01/2026-01/31/2027
2025 Early-Stage Investigator Neurology Research Award $35,000
Mayo Clinic Arizona
Application of multimodal biomarkers to identify a Lewy body disease neurodegeneration index

Shannon Chiu (Co-I) 01/01/2026-01/31/2027
(Mitropanopoulos) $35,000

2025 Early-Stage Investigator Neurology Research Award
Mayo Clinic Arizona
Characterizing EEG features in autopsy cohort of dementia with Lewy bodies

Shannon Chiu (Co-I) 07/01/2025-07/01/2027
(Choudhury) $60,000
Arizona Alzheimer's Consortium and Arizona Alzheimer's Disease Research Center (ADRC)
Sponsored Developmental Project Grant Program
Integrating proteomics and AI in Lewy Body Disease biomarker discovery

Shannon Chiu (PI) 06/01/2022-05/31/2027
1K23AG073525-01A1 $781,028
NIH
Neurodegeneration and Neuronal Fluctuations in DLB and AD

Shannon Chiu (PI) 04/01/2024-present
Lewy Body Dementia Association (LBDA) $12,500 Annually
Research Center of Excellence (RCOE)
Arizona Collaborative LBDA RCOE

Erika Driver-Dunckley (PI) 08/15/2024-07/31/2029
R01 NS139383 $470,765
National Institute of Neurological Disorders and Stroke
Risk and Resilience, Clinical presentation, and Biomarker Profiles of Chronic Traumatic Encephalopathy and Related Dementias: The DIAGNOSE CTE Research Project II

Oana Dumitrascu (PI) 08/01/2025-01/31/2027
SPA00008275 $100,000
Arizona State University
Retinal Imaging-Based Deep Learning Model to Predict Alzheimer's Disease in Presymptomatic Stages

Mary Ellen Koran (PI) 04/01/2025-05/31/2029
K76 AG088554 $1,266,433
National Institute on Aging
Genetic architecture of age of onset of amyloid positivity: Integrating imaging and genetic tools to identify novel drivers of disease

Dona Locke (Co-I) 09/30/2020-03/31/2026
R01 AG069453-05 (Reiman) $1,271,104
National Institute on Aging
APOE in the Predisposition to, Protection from and Prevention of Alzheimer's Disease

Dona Locke (Co-I) 07/2021-06/2025
ADHS14-052688 (Woodruff) $3,724,000
Arizona Department of Health Services
Normal and Pathological Aging (Preclinical Alzheimer's Disease)

Shyamal Mehta (PI) 09/01/2024-06/30/2029
R01 AG086533 $118,970
National Institute on Aging

Identifying Targets for Fall-prevention Rehabilitation in People with Parkinson's Disease

Shyamal Mehta (PI) 01/06/2026-12/31/2026
PPMI 060 $117,847
Michael J Fox Foundation for Parkinson's Research
The Parkinson's Progression Markers Initiative (PPMI)

Gaurav Pradhan (Co-I) 09/30/2020-03/31/2026
R01 AG069453-05 (Reiman) $1,271,104
National Institute on Aging
APOE in the Predisposition to, Protection from and Prevention of Alzheimer's Disease

Bryan Woodruff (PI) 09/30/2020-03/31/2026
R01 AG069453-05 $1,271,104
National Institute on Aging
APOE in the Predisposition to, Protection from and Prevention of Alzheimer's Disease

Bryan Woodruff (PI) 07/01/2021-06/30/2027
ADHS14-052688 $3,724,000
Arizona Department of Health Services
Normal and Pathological Aging (Preclinical Alzheimer's Disease)

Robert Mercer (PI) 09/30/2025-09/29/2027
R21NS146741 $386,650
NIH (NINDS) R15 REAP
Elacridar: Identification of the molecular target relevant to its anti-prion effects and its application to other protein misfolding neurodegenerative diseases

Elizabeth Hull (PI) and Kathryn Leyva (Co-PI) 07/01/2025-06/30/2026
Arizona Alzheimer's Consortium $30,000
Non-coding RNA regulation of the progranulin gene during the inflammatory response in Alzheimer Disease

Marisa Menchola (Co-I) 07/01/2025-06/30/2026
Arizona Alzheimer's Consortium $6,630 Subaward Project
(Subaward from Banner Alzheimer's Institute/The University of Arizona)
Clinical Profiles and Predictors of Cognitive Performance in Plasma P-tau217 Positive Individuals in Memory Clinic and Research Settings

Nancy Bae (PI) & Mark Swanson (Co-I) 07/01/2025-06/30/2026
Arizona Alzheimer's Consortium $12,395
Oxidative Stress Causes Increased Amyloid Peptide Levels through Telomeric Protein, RAP1

Joao Carvalho-de-Souza (PI) & Layla Al-Nakkash (Co-I) 07/01/2025-06/30/2026
Arizona Alzheimer's Consortium $22,782
Studies on Kv6.1 silent subunit expression and function in hippocampal neurons during Alzheimer's disease

Tiffany Hughes (PI) 07/01/2025-06/30/2026
Alison de la Montaigne (Co-I), Marisa Menchola (Co-I), $10,317
Stephanie Christensen (Co-I), Patrice Ayala (Co-I)

Arizona Alzheimer's Consortium
The Opening Minds through Art Program with Unhoused Older Adults: An Implementation Pilot Study

Layla Al-Nakkash (PI), Joao Carvalho-de-Souza (Co-PI) 07/01/2025-06/30/2026
Arizona Alzheimer's Consortium $7,300
Assessment of inflammatory pathways involved in the brain-intestinal axis in western diet induced Alzheimer's pathology.

Elizabeth Hull (PI) & Kathryn Leyva (Co-I) 07/01/2025-06/30/2026
Arizona Alzheimer's Consortium $9,912
Elucidating a mechanistic link between progranulin & lysosomal function in Alzheimer Disease

Garilyn Jentarra (PI), T. Bucky Jones (Co-PI) 07/01/2025-06/30/2026
Arizona Alzheimer's Consortium $44,385
Determination of polymicrobial burden in two postmortem brain regions in AD patients and controls with varying levels of AD-related pathology and cognitive status

Kathryn Lawson (PI) & Kimberly Bussey (Co-PI) 07/01/2025-06/30/2026
Arizona Alzheimer's Consortium $12,894
Investigating the Role of Stress Hormones on Astrocyte Neurogenics

Mark Olsen (PI) & Volkmar Weissig (Co-I) 07/01/2025-06/30/2026
Arizona Alzheimer's Consortium $7,230
Design, Synthesis and Testing of Novel Compounds for the Treatment of Alzheimer's Disease

Minsub Shim (PI) 07/01/2025-06/30/2026
Elizabeth Hull (Co-PI), Delrae Eckman (Co-PI) $12,390
Arizona Alzheimer's Consortium
The periphery of Alzheimer's disease: cross-talks between degenerating brain and peripheral tissues

Mark Swanson (PI) & Nancy Bae (Co-I) 07/01/2025-06/30/2026
Arizona Alzheimer's Consortium $12,395
Molecular mechanisms of altering gamma secretase activity by modulatory proteins

Marisa Menchola (Co-I) 07/01/2025-06/30/2026
Arizona Alzheimer's Consortium $13,260 Subaward Project
(Subaward from Banner Alzheimer's Institute/The University of Arizona)
Partnering with Primary Care for Clinical Implementation of Blood-Based Biomarkers to Facilitate Early Detection and Access to Disease-Modifying Treatments for Alzheimer's Disease

Marisa Menchola (Co-I) 02/01/2025-06/30/2025
Arizona Alzheimer's Consortium $5,364 Subaward Project
(Subaward from Banner Alzheimer's Institute)
Hispanic Outreach, Recruitment and Retention Program

Ann Revill (PI) 09/01/2024-08/31/2027
R15HL175526 $421,800
NIH R15 REAP
Effects of chronic intermittent hypoxia on cholinergic modulation at hypoglossal motoneurons

Volkmar Weissig (Co-PI) 07/26/2024-12/31/2025
Arizona Biomedical Research Commission $49,602 Total Subaward
(Subaward from AZ Veterans Research and Education Foundation)
Validation & Development of Nanoliposomes for Neuroprotection in Stroke

Ann Revill (PI) 07/01/2024-06/30/2026
Arizona Alzheimer's Consortium $120,000
FY25 Developmental Project
Physiological and anatomical hallmarks associated with intermittent hypoxia and aging – insights into respiratory dysfunctions associated with Alzheimer's disease

Garilyn Jentarra (PI) & T. Bucky Jones (Co-PI) 07/01/2024-06/30/2025
Arizona Alzheimer's Consortium $65,000
Exploring the association between the bacterial content of blood and brain tissue, and its influence on AD pathology

Minsub Shim (PI) and Layla Al-Nakkash (Co-PI) 07/01/2024-06/30/2025
Arizona Alzheimer's Consortium $26,830
Metabolic intervention of Alzheimer's disease: Ketone bodies as a potential strategy to improve energy metabolism in the aging brain

Elizabeth Hull (PI) and Kathryn Leyva (Co-I) 07/01/2024-06/30/2025
Arizona Alzheimer's Consortium $24,930
The role of progranulin in the inflammatory response in Alzheimer's disease

Layla Al-Nakkash (PI) and Minsub Shim (Co-I) 07/01/2024-06/30/2025
Arizona Alzheimer's Consortium $23,240
Assessment of metabolomic pathways involved in the brain-intestinal axis in western diet induced Alzheimer's pathology

Tamara Turner (PI) and Alison de la Montaigne (Co-I) 07/01/2024-06/30/2025
Arizona Alzheimer's Consortium $20,000
Effects of Dementia on Couplehood: An Occupational Perspective

Heather Smith (PI) 12/01/2023-11/30/2025
Impetus Grants $33,000
Unlocking the senescence-resistant adaptations of long-lived giant tortoises to develop a novel model organism for aging studies

Tiffany Hughes (Co-I) 08/28/2023-04/30/2031
5R37AG023651-21 $346,989 Subaward Project
NIH R37 (Subaward from University of Pittsburgh)
Mild Cognitive Impairment: A Prospective Community Study

Kimberly Bussey (Co-Investigator) 08/01/2023-06/30/2027
1R25HG012330-01 $25,232 Subaward Project
NIH R25 (Subaward from Arizona State University)
Training in Genomics Research (TiGeR)

McCarthy, M. & Cerino, E. (Mentor/Preceptor) 06/01/2026-05/31/2031
T32GM161965 (De Heer) $1,761,259 Direct Costs
NIH/NIGMS
G-RISE at Northern Arizona University

McCarthy, M. (Co-I) 09/01/2024-08/31/2027
U54CA143925 (Hammer/Godfrey) $180,000
Partnership for Native American Cancer Prevention Developing a Culturally Responsive Psychosocial Support Intervention for American Indian Adults with Co-morbid Type 2 Diabetes and Cancer

McCarthy, M., Cerino, E., McCoy, M. (Co-PIs) 07/01/2023-06/30/2026
Arizona Alzheimer's Consortium /AZDHS $464,000
Development of Tailored Technologies and Resources to Identify and Support Rural Caregiver-Receiver Dyads with Mild Cognitive and Subjective Cognitive Decline: The Northern Arizona Memory Study

McCarthy, M. (Consultant) 01/01/22-12/31/27
NIH-NINR R01NR020184 (Bakas) $3,876,661
Telehealth Assessment and Skill-Building Intervention for Stroke Caregivers (TASK III)

McCoy, M. (NAU Site PI) 7/1/2024-6/30/2029
US HRSA 1 U1QHP53053-01-00 (Fain) $4,923,639
HRSA Arizona Geriatrics Workforce Enhancement Program

Cerino, E. (PI) 07/01/2023-06/30/2025
Pilot Project Program through NIMHD $100,000
(U54MD012388; Baldwin)
The Roles of Daily Stressor Control and Social Determinants of Health in Cognitive Aging: Examining Modifiable Contributors to Cognitive Health Disparities in Daily Life

Cerino, E. (Co-I) 07/01/2022-06/30/2027
NIH-NIA U19AG051426 (Almeida) $3,992,718
Changes in Daily Stress and Well-Being. Renewal for the National Study of Daily Experiences MIDUS Daily Diary Project

Cerino, E. (Co-I, Lead Faculty Mentor) 06/01/2024-05/31/2025
NIH institutional Champion Award (1OT20D028395) $75,000
Institutional Champion for NIH's All of Us Research Program

Cerino, E. (Co-I) 07/01/2023-06/30/2025
Social Sciences & Humanities $74,572
Research Council of Canada (Rush)
Day-to-Day Influence of Climate Change Distress on Daily Well-Being and Climate Action Behaviors

McCoy, M. (PI) 07/01/2025-06/30/2025
Kellenberger + Tollefson Center for LGBTQ+ Philanthropy $10,000
(Beatitudes Campus)
Arizona LGBTQ+ Aging Survey

Emily Cope (Research Project Lead; Baldwin PI) 09/2022 – 08/2027
Southwest Health Equity Research Collaborative $27,669,552 Total Project
NIH/NIMHD $1,976,000 Research Project
Research Project #3 Title: Evaluation of soluble fiber as a strategy to decrease asthma morbidity in underserved populations

Emily Cope (PI) 07/01/2025-06/30/2026
CTR040636 (Cope) $80,000 Direct Costs
Arizona Alzheimer's Consortium Alzheimer's /AZDHS
Microbiome modulation of vagal afferent signaling

J. Gregory Caporaso, Co-I 09/01/2021-08/31/2026
2125088 $3,000,000 Direct Costs
National Science Foundation; PI: Jane Marks
Discovering in reverse – using isotopic translation of omics to reveal ecological interactions in microbiomes

Emily Cope, J. Gregory Caporaso (Mentor/Preceptor) 06/01/2026-05/31/2031
T32GM161965 (De Heer) $1,761,259 Direct Costs
NIH/NIGMS
G-RISE at Northern Arizona University

Matthew Huentelman (Co-I) 05/01/2020 – 08/31/2025
R01 AG067781 (Rogalski) $397,866
NIH via University of Chicago
Cognitive SuperAging: A model to explore resilience and resistance to aging and Alzheimer's disease

Matthew Huentelman (Co-I) 10/01/2021-03/31/2027
1R01AG069453-01 (Reiman/Caselli/Su/Chen/Langbaum) $725,418
NIH/NIA via Banner Health
APOE in the Predisposition to, Protection from and Prevention of Alzheimer's Disease

Matthew Huentelman (Co-I) 11/29/2023 – 05/31/2026
U19 AG073153 (Rogalski/Geula) $2,596,540
NIH/NIA via University of Chicago
Study to uncover pathways to exceptional cognitive resilience in aging (SUPERAging)

Matthew Huentelman (Co-I) 09/05/2021 – 06/30/2026
1 P30 AG072980-01 (Langbaum) $84,470
NIH via Banner Health
Arizona Alzheimer's Disease Core Center

Matthew Huentelman (Co-I) 09/01/2021 – 08/31/2026
1U19 AG056169-01A1 (Barnes) $18,509,311
NIH via University of Arizona
Precision Aging Network: Closing the Gap Between Cognitive Healthspan and Human Lifespan

Matthew Huentelman (Co-I) 09/01/2024 – 08/31/2026
IOS-2207023 (sub-774332) (Madhavan) $105,118
NSF via University of Arizona

Neural Stem Cell Mechanisms of Resilience across the lifespan

Matthew Huentelman (Co-I) 06/15/2022 – 03/31/2027
R01AG077444 (Mesulam) $1,562,381
NIH via Northwestern University
Asymmetric neurodegeneration and language in primary progressive aphasia

Matthew Huentelman (Co-I) 08/15/2022 – 04/30/2027
R01AG068098 (Grilli) $199,369
Tracking autobiographical thoughts: a smartphone-based approach to identify cognitive correlates of Alzheimer's disease biomarkers and risk factors in clinically normal older adults.
NIH via University of Arizona

Matthew Huentelman (Co-I) 09/18/2024 – 08/31/2029
R01AG089050 (Seidler) $89,571
NIH via University of Florida
Neural Correlates of Cognitive-Motor Interactions in ADRD Gait

Matthew Huentelman (Co-I) 09/01/2023 – 05/30/2030
2UG3DO23313-10 (Mitchel/ D'Sa) $138,719
NIH via Rhode Island Hospital
Assessing the cumulative risk of early life exposures on child physical health and neurodevelopment

Matthew Huentelman (PI) 04/15/2024 -06/30/2025
2024-04-01 $151,990
CSNK2A1 Foundation
Characterization of CSNK2A1 disease causing variants in two-dimensional differentiated neurons.

Matthew Huentelman (Co-I) 09/02025- 08/2027
1DP2MH140150 (Lewis) $136,193
NIH via Arizona State University
Individually measured endophenotypes to advance computational translation in mental health

Matthew Huentelman (Co-PI) 08/2025-12/31/2026
NA (Jensen) $106,028
TGen Foundation
Organoid-Based Evaluation of AAV-HSC Therapeutic Vectors for Usher Syndrome USH2A

Matthew Huentelman (Co-I) 05/2025-02/20258
R01AA030256 (Bortelato) $96,526
NIH via University of Florida
Disentangling the biological links of violence and alcohol use

John Fryer (Co-I) 09/2020 – 08/2027
5U2CCA252973 (Willman & Trent) $6,781,247
NIH via University of New Mexico
Engagement of American Indians of Southwestern Tribal Nations in Cancer Genome Sequencing

Iganzio Piras (Co-I) 10/01/2021-03/31/2027

1R01AG069453-01 (Reiman/Caselli/Su/Chen/Langbaum) $84,470
NIH/NIA via Banner Health
APOE in the Predisposition to, Protection from and Prevention of Alzheimer's Disease

Ignazio Piras (Co-I) 07/01/2021 – 06/30/2026
1P30AG072980 (Reiman) $84,470
NIH via Banner Health
Arizona Alzheimer's Disease Research Center (ADRC)-Core C

Ignazio Piras (Co-I) 04/15/2022-02/28/2027
R01 DK120127015 (DiStefano) $3,690,587
NIH/NIDDK
Extracellular vesicle cargo and risk of NAFLD and NASH in youth

Ignazio Piras (Co-I) 06/15/2022 – 03/31/2027
R01AG077444 (Mesulam) $1,562,381
NIH via Northwestern University
Asymmetric neurodegeneration and language in primary progressive aphasia

Ignazio Piras (Investigator) 09/01/2024 – 08/31/2026
2207023 (Madhaven) $156,309
NSF via University of Arizona
Neural Stem Cell Mechanisms of Resilience Across the Lifespan

Ignazio Piras (Investigator) 09/01/2021 – 08/31/2026
1U19 AG056169-01A1 (Barnes) $18,509,311
NIH via University of Arizona
Precision Aging Network: Closing the Gap Between Cognitive Healthspan and Human Lifespan

Ignazio Piras (Co-I) 05/01/2020 – 08/31/2025
R01 AG067781 (Rogalski) $397,866
NIH via University of Chicago
Cognitive SuperAging: A model to explore resilience and resistance to aging and Alzheimer's disease

Kendall Van Keuren- Jensen (PI) 06/01/2026 -05/31/2029
ASAP-027477 $8,504,248
Aligning Science Across Parkinson's /Michael J Fox Foundation
Investigate the impact of Parkinson's disease lysosomal risk variants on lysosomal function and alpha-synuclein clearance across CNS cell types

Kendall Van Keuren- Jensen (Co-I) 01/01/2026 – 12/31/2027
0435-06-249131 (Reiman) $334,950
Nomis Foundation via Banner Health
A Public Resource of RNA Sequencing Data from Different Human Brain Cells and Regions

Kendall Van Keuren- Jensen (PI) 01/01/2026 – 12/31/2026
MJFF-028687 $60,000
Aligning Science Across Parkinson's /Michael J Fox Foundation

Global Parkinson's Genetics Program (GP2) -2026 Operations Committee Award

Kendall Van Keuren-Jensen (Co-I) 09/01/2025-08/31/2026
1R01NS12331 (Sattler) $288,800
NIH via St. Joseph's Hospital and Medical Center
Microglia contribution to disease pathogenesis in C9orf72 ALS/FTD

Kendall Van Keuren-Jensen (PI) 08/01/2025 – 09/30/2026
NA $880,792
TGen Foundation
Organoid-Based Evaluation of AAV-HSC therapeutic vectors for Usher Syndrome (USH2A)

Kendall Van Keuren-Jensen (Co-I) 04/01/2025 – 03/30/2027
HT94252410195 (Sattler) $235,322
DoD via St. Joseph's Hospital and Medical Center
The role of TDP-43 associated cryptic exon inclusion in KALRN on C9orf72-mediated cortical neurodegeneration

Kendall Van Keuren-Jensen (Co-I) 06/01/2023-05/31/2026
R24NS132738 (Craig) $2,250,003
NIH
A Large-scale Extracellular Vesicle RNA-seq Resource for Parkinsons Disease

Kendall Van Keuren-Jensen (Co-I) 09/01/2022-07/31/2027
R01D133847 (Das) $650,121
NIH via Mass General Hospital
Characterization of beta-cell-specific extracellular vesicle cargo as functional biomarkers for type 1 DM disease (Teddy)

Alexander, Gene E. (MPI) 8/01/2019 – 04/30/2026 NCE
R01 AG064587 (MPIs: Alexander, Bowers, Woods) $3,797,247
NIA
Revitalizing Cognition in Older Adults at Risk for Alzheimer's Disease with Near-Infrared Photobiomodulation

Alexander, Gene E. (Core Leader) 09/01/2021 - 06/30/2026
P30AG072980 (PI: Langbaum, Core Leader: Alexander) $1,223,160 TC UA Sub
NIA
Arizona Alzheimer's Disease Research Center-Biomarker Core

Alexander, Gene E. (MPI) 04/01/2022 - 03/31/2027
R01AG072445 (MPIs: Alexander, Raichlen, Klimentidis) $3,074,021
NIA
Inactivity, Sedentary Behavior, and the Risk for Alzheimer's Disease in Middle Aged to Older Adults

Alexander, Gene E. (PI: Alexander) 07/01/2025 – 06/30/2026
State of Arizona $33,904
Network Imaging and Lifestyle Biomarkers for Evaluating Vascular Contributions to Brain Aging and Alzheimer's Disease

Alexander, Gene E. (Co-I) 08/15/2021-05/31/2027 NCE
R01AG070987 (PI: Weinkauf) $4,900,635
NIA
Extracranial Carotid Atherosclerosis Contributions to Cognitive Impairment and Alzheimer's Disease Risk

Alexander, Gene E. (Co-I) 07/01/2022-06/30/2027
R01AG068098 (MPIs: Andrews-Hanna, Grilli) $4,600,829
NIA
Tracking autobiographical thoughts: a smartphone-based approach to identifying cognitive correlates of Alzheimer's disease biomarkers and risk factors in clinically normal older adults

Altbach, Maria (PI) 09/01/2021-08/31/2027
R01 HL159200 (Altbach, DeMarco, Li, Parker, Saloner) $6,156,398
NIH/NHLBI
Multi-Center Implementation and Validation of Efficient Magnetic Resonance Imaging and Analysis of Atherosclerotic Disease of the Cervical Carotid

Altbach, Maria (PI) 07/01/2021-06/31/2026
CTR056039 (Altbach, Bilgin) $750,000
Arizona Biomedical Research Commission
Development of MRI Biomarkers for Improved Risk Stratification of Patients with Carotid Atherosclerosis to Prevent Stroke

Altbach, Maria (PI) 08/01/2022- 04/30/2027
U01 EB031894 (Altbach, Deshpande, Wu) $3,533,177
NIH/NIBIB
Quantitative MRI and Deep Learning Technologies for Classification of NAFLD

Altbach, Maria (Co-I) 04/01/2024- 03/31/2027
RFGA2023-008-12 (Chen) $750,000
Arizona Biomedical Research Commission
Development of high-performance, low cost, low-field lung magnetic resonance imaging (MRI) to improve care in lung cancer and respiratory illnesses

Barnes, Carol (PI) 05/01/2023-04/30/2027
R01 AG081767-01 $2,895,716
NIH/NIA
Frontal and Temporal Lobe Interactions in Rat Models of Normative Aging and Alzheimer's Disease

Barnes, Carol (PI) 05/01/2022-04/30/2027
T32 AG044402 $1,455,971
NIH/NIA
Postdoctoral Training, Neurobiology of Aging and Alzheimer's Disease

Barnes, Carol (PI) 09/01/2021-12/31/2026
R01 AG003376 $4,821,974
NIH/NIA
Neurobehavioral Relations in Senescent Hippocampus

Barnes, Carol (PI) 09/01/2021-08/31/2026
U19 AG065169 $59,988,951
NIH/NIA
Precision Aging Network: Closing the Gap Between Cognitive Healthspan and Human Lifespan

Barnes, Carol (PI) 05/01/2021-04/30/2027
R01 AG072643 $5,719,524
NIH/NIA
NPTX2: Preserving memory circuits in normative aging and Alzheimer's Disease

Bartlett, Mitchell J. PhD (PI) 06/15/2026-05/31/2031
K99/R00 1K99NS141888-01A1 (Bartlett) $1,004,040
NIH/NINDS via University of Arizona
Unlocking the Brain's Lymphatic System: A Novel Surgical and a Non-Invasive Approach to Treating Alzheimer's Disease

Bartlett, Mitchell J. PhD (CoI) 09/01/2025-08/31/2027
Advanced Research Projects Agency-Health (ARPA-H) $1,776,918
AY2AX000090 (R. Witte)
ARPA-H via University of Arizona
Game Changing Quantitative and Targeted Multimodal Lymphatic Imaging to Go

Bartlett, Mitchell J. PhD (PI) 09/01/2025-08/31/2028
Burroughs Wellcome Fund $60,000
Postdoctoral Enrichment Program (BWF-PDEP) 1465398 (Bartlett)
BWF via University of Arizona
Cervical Lymphatic Dysfunction in Alzheimer's Disease: A Novel Target to Improve Amyloid-Beta Clearance and Cognitive Function

Bartlett, Mitchell J. PhD (CoI) 07/01/2025-06/30/2026
Arizona Alzheimer's Consortium (AAC) (Hutchinson) $47,000
AAC via University of Arizona
Advanced dMRI applications to detect microscale pathology and glymphatic lymphatic pathophysiology in the TgF344-AD rat model

Bartlett, Mitchell J. PhD (PI) 07/01/2025-06/30/2026
Arizona Alzheimer's Consortium (AAC) (Bartlett) $30,000
AAC via University of Arizona
Pathophysiological characterization of the brain's lymphatics in a transgenic rodent model of Alzheimer's disease

Bartlett, Mitchell J. PhD (PI) 06/01/2026-05/31/2028
Highberger Research Award (Bartlett) $5,000
Department of Surgery, University of Arizona via University of Arizona
Impact of Secondary Lymphedema on Alzheimer's disease and the Development of a Microsurgical Approach to Treatment

Bilgin, Ali (Co-I) 10/01/2025-09/30/2027
(Witte) $1,776,918
Advanced Research Projects Agency - Health
Game Changing Quantitative and Targeted Multimodal Lymphatic Imaging to Go

Bilgin, Ali (Co-I) 09/01/2022-04/28/2027
1R01EB032674 (Saranathan) $2,191,177
NIH/NIBIB via University of Massachusetts Amherst
Next-Generation Thalamic Nuclei Visualization and Segmentation Methods

Bilgin, Ali (Co-I) 04/01/2024-03/31/2027
NLID 89275 (Chen) $750,000
Arizona Biomedical Research Centre
Development of high-performance, low-cost, low-field lung MRI to replace CT and improve care of lung cancer and respiratory illnesses

Bilgin, Ali (Co-I) 08/01/2022-04/28/2027
1U01EB031894 (Altbach/Deshpande/Wu) $1,344,284
NIH/NIBIB via University of California Los Angeles
Quantitative MRI and Deep Learning Technologies for Classification of NAFLD

Bilgin, Ali (Co-PI) 07/01/2021-06/30/2026
CTR056039 (Altbach/Bilgin) $749,921
Arizona Biomedical Research Centre
Development of Biomarkers for Improved Risk Stratification of Patients with Carotid Atherosclerosis to Prevent Stroke

Bilgin, Ali (Co-I) 09/01/2021-08/31/2026
U19AG065169 (Barnes) $60,014,605
NIH/NIA
Precision Aging Network: Closing the Gap Between Cognitive Healthspan and Human Lifespan

Chen, Nan-kuei (Co-I) 09/30/2021 – 08/31/2027
NIH U19-AG065169 (Barnes) $60,014,605
NIH/NIA
Precision Aging Network: Closing the Gap Between Cognitive Healthspan and Human Lifespan

Chen, Nan-kuei (PI) 08/05/2024-07/31/2027
NIH R21 NS137573 (Chen) $440,640
NIH/NINDS
Investigating electromagnetic field-based neuromodulation of slow-wave brain activity and glymphatic system

Chen, Nan-kuei (Co-I) 05/01/2020-01/31/2027
NIH R01 AG062543 (Chou) $3,629,382
NIH/NIA
Enhancement of Hippocampal Plasticity Using Repetitive Transcranial Magnetic Stimulation

Chou, Ying-hui (Co-I) 09/01/2020-06/30/2027
U01EB028662 (Witte) $3,434,477
NIH/NIBIB
4D Transcranial Acoustoelectric Imaging for High Resolution Functional Mapping of Neuronal Currents

Chou, Ying-hui (PI) 05/01/2020-01/31/2027
R01 AG062543 (Chou) $3,468,515

NIH/NIA
Enhancement of hippocampal plasticity using repetitive transcranial magnetic stimulation

Chou, Ying-hui (Contact PI) 07/01/2026-06/30/2028
CAMI Core (Chou and Agudelo) $150,000
McKnight Brain Research Foundation
Targeting Sleep to Preserve Memory: Accelerated Theta Burst Stimulation and At-Home Sleep EEG to Enhance Cognitive Health in Aging

Chou, Ying-hui (Co-I) 09/01/2024-08/31/2027
HT94252410981 (Killgore) $3,069,903
DoD
Effectiveness of Transcranial Magnetic Stimulation of the Default Mode Network to Improve Sleep

Chou, Ying-hui (Co-I) 07/01/2025-06/30/2029
LTR DTD 061625 (Zhou) $1,200,000
US Department of Veterans Affairs
Role of Carotid Disease in Cognitive Impairment and Dementia

Chou, Ying-hui (Co-I) 07/01/2024-06/30/2027
R21 NS137573 (Chen) $437,520
NIH/NINDS
Investigating electromagnetic field-based neuromodulation of slow-wave brain activity and glymphatic system

Cowen, Stephen (Co-I) 05/01/2023-04/30/2027
R01 AG081767-01 (Barnes) $2,895,716
NIH/NIA
Frontal and Temporal Lobe Interactions in Rat Models of Normative Aging and Alzheimer’s Disease

Cowen, Stephen (PI) 09/15/2021 - 08/31/2026
R01NS123424 $1,833,908
NIH/NINDS
Control of the Time Course of Dopamine Release Through Optimized Electrical Brain Stimulation

Cowen, Stephen (PI) 07/01/2026-06/30/2027
AAC FY27 (Cowen) $58,128
Arizona Alzheimer’s Consortium
TgF344-AD rat model of Alzheimer's Disease, Histopathological markers in relation to cognitive performance, and high-resolution diffusion MRI variables.

Cowen, Stephen (Co-I) 4/15/24 - 03/31/29
R25 NIH/NIA (R25AG086126) (Rodgers) $1,885,436
Diversity in Research Education in Aging Medicine and Science

Cowen, Stephen (Co-I) 8/01/24 - 7/31/29
NIH/NINDS (R25NS138018) (Rodgers) $1,337,340
Neuroscience Diversity to Elevate Education and Research Development

Cowen, Stephen (Co-I) 9/30/2020-6/30/26
U01 NIBIB (U01EB029834) (Witte) $3,608,394
4D Transcranial Acoustoelectric Imaging for High Resolution Functional Mapping of Neuronal Currents

Cowen, Stephen (Co-I) 8/15/2021-05/31/26
P30 NIH-NIDA (P30DA051355 ID(41986)) (Porreca) $7,667,187
The Center of Excellence in Addiction Studies (CEAS)

Gaffney, Kevin (Co-PI) 05/01/2020-04/30/2026 (NCE)
U01 AG063768 (Rodgers) $6,108,279
NIH/NIA via University of Arizona
IND Enabling Studies for RASRx1902, a novel Mas receptor agonist, for treatment of cognitive impairment in patients at risk for Alzheimer's disease

Garcia, David O. (PI) 06/01/2025-06/30/2026
4279450 / 024125-00001 $30,000
Arizona Alzheimer's Consortium & Arizona Department of Health Services

Hutchinson, Elizabeth (PI) 03/01/2023 – 02/28/2028
R01AG079280 $1,199,716
NIH
Joint Estimation Diffusion Imaging (JEDI) for Improved Tissue Characterization and Neural Connectivity in Aging and Alzheimer's Disease

Hutchinson, Elizabeth (PI) 07/01/2024-06/30/2028
1108337-6681-67661 (Juliano) $24,641
Henry M. Jackson Foundation, DoW
MTB12 Translational Therapeutic Ferret Core

Hutchinson, Elizabeth (Co-I) 03/01/2023 - 02/28/2028
R01 MH135267 (Gothard) $2,676,253
NIH
Maturation of social and non-social reward processing in the adolescent amygdala and orbitofrontal

Hutchinson, Elizabeth (PI) 05/01/2022-04/30/2022
R01 AG073230 (Pires) $826,690
NIH
Role of Endothelial K+ Channels in Age-Related Dementia

Kieler, Aneta (PI) 03/01/2025-06/30/2026
FY24 RII Core Facilities Pilot Program $6,331
Research: Innovation and Impact
Interaction between the BDNF genotype and treatment response to noninvasive brain stimulation in the language variant of Alzheimer's disease.

Kielar, Aneta (PI) 07/01/2024-06/30/2026
Arizona Department of Health and Human Services $120,000 Total Project

via Arizona Alzhemers Consortium & Arizona Alzheimer's Research Center (ADRC)
Using Noninvasive Electrical Brain Stimulation to Improve Language in the Logopenic variant of Alzheimer's Disease

Kielar, Aneta (PI) 01/15/2024-12/31/2028
NIH/NIA $3,755,306
Enhancing Language in Logopenic Primary Progressive Aphasia with Targeted Phonological Treatment and Transcranial Direct Current Stimulation (tDCS)

Pires, Paulo (MPI) 05/01/2022-04/30/2027
R01 AG073230 (Behringer) $3,376,180
NIH/NIA via Loma Linda University
Role of Endothelial K+ Channels in Age-Related Dementia

Pires, Paulo (Co-I) 08/01/2023-05/31/2028
R01 HD111125 (PI: Erickson) $3,655,377
NIH/NICHHD via The University of Arizona
Oxytocin sensitivity and postpartum hemorrhage: testing genetic and epigenetic biomarkers for improving maternal morbidity

Rodgers, Kathleen (PI) 07/01/2025–05/31/2030
2R01AG064228-07A1 (Rodgers) $700,519
NIH via University of Southern California
Endothelial Progenitor Cells and Neurovascular Injury in the Aging Brain

Rodgers, Kathleen (PI) 09/06/2024–08/31/2029
1R25NS138018-01 (Rodgers) $1,337,340
NIH/NINDS
Neuroscience Diversity to Elevate Education and Research Development

Rodgers, Kathleen (PI) 04/15/2024–03/31/2029
1R25AG086126-01 (Rodgers) $1,441,340
NIH/NIA
Diversity in Research Education in Aging Medicine and Science

Rodgers, Kathleen (PI) 09/01/2023–08/31/2028
T32AG082631 (Rodgers) $600,213
NIH/NIA
Translational Research in Alzheimer's Disease and Related Dementias (TRADD)

Rodgers, Kathleen (Project 3 Lead) 06/01/2021 – 05/31/2027 (NCE)
2P01AG026572-5419 (Brinton) $1,839,375
NIH/NIA
Perimenopause in Brain Aging and Alzheimer's Disease | Project 3: Peripheral Immune Activation on the road to Development of Alzheimer's Disease: Therapeutic Targets and Windows

Rodgers, Kathleen (Co-Investigator) 08/15/2019 – 04/30/2027 (NCE)
5R01AG063826 (Brinton) $37,329,334
NIH/NIA
Allopregnanolone as Regenerative Therapeutic for Alzheimer's: Phase 2 Clinical Trial

Ryan, Lee (Co-I) 09/01/2023-08/31/2027
TP220092 (Joseph) $3,004,651
DoD
Angiotensin-(1-7): A Treatment for Neuropsychological and Memory Impairments Following Moderate to Severe Traumatic Brain Injury

Ryan, Lee (PI) 07/01/2025-06/30/2026
Arizona Department of Health Services, AAC $63,240
The impact of APOE E4 on episodic and autobiographical memory: Episodic and semantic detail generation across the adult lifespan

Ryan, Lee (Project Lead) 09/01/2021-08/31/2026
U19 AG065169 (Barnes) $59,998,952
NIH/NIA
Precision Aging Network: Closing the Gap Between Cognitive Healthspan and Human Lifespan

Savir-Baruch, Bital (PI) 08/15/2021-05/31/2027
R01 AG070987 $4,800,000
Extracranial Carotid Atherosclerosis Contributions to Cognitive Impairment and Alzheimer's Disease Risk

Savir-Baruch, Bital (Co-I) 09/01/2021-08/31/2027
R01 HL159200 $6,900,000
(MPI: Saloner, Parker, Altbach, De Marco, Li, Deshpande)
Multi-Center Implementation and Validation of Efficient Magnetic Resonance Imaging and Analysis of Atherosclerotic Disease of the Cervical Carotid

Shaik, Shabana M. (PI) 06/01/2026-05/31/2028
PANDA Foundation $300,000
Gut microbiome-a link between Down Syndrome and Alzheimer's Disease

Su, Judith (PI) 01/01/2023-12/31/2027
NSF CAREER Award $580,000
National Science Foundation
CAREER: Bioinspired Optical Sniffer Based on Microtoroid Resonators and Science and Technology Convergence

Su, Judith (PI) 09/01/2024-09/30/2027
U.S. Army Combat Capabilities Development Command (DEVCOM) $2,075,000
Title: FORWARD: FLOWER-based Optical Resonators for Widely Applicable Reagent Detection

Trouard, Theodore (PI) 03/2023-03/2026
NIH S10 OD032166 (Trouard) $2,000,000
3T MRI scanner for Advanced Brain Imaging

Trouard, Theodore (Co-I) 09/2021-02/2026
NIH U19AG065159 (Barnes) $59,998,952
Closing the Gap Between Cognitive Healthspan and Human Lifespan

Trouard, Theodore (Co-I) 09/2021-06/2026
NIH P30AG072980 (Alexander/Reiman) $1,223,160
Arizona Alzheimer's Disease Research Center

Weinkauf, Craig (PI) 08/15/2021-05/31/2027
R01AG070987 (Weinkauf) $4,800,000
NIH/NIA via University of Arizona
Extracranial Carotid Atherosclerosis Contributions to Cognitive Impairment and Alzheimer's Disease Risks

Weinkauf, Craig (Co-I) 09/01/2021-08/31/2027
R01 HL159200 $6,156,398
(Altbach, DeMarco, Li, Parker, Saloner, Deshpande)
NIH/NHLBI
Multi-Center Implementation and Validation of Efficient Magnetic Resonance Imaging and Analysis of Atherosclerotic Disease of the Cervical Carotid.

Zhou, Wei (PI) 05/01/2025-04/30/2029
1I01CX002260-01A2 (Zhou) $1,200,000
Veteran Health Administration
Role of Carotid Disease in Cognitive Impairment and Dementia

Zhou, Wei (MPI) 04/01/2023-03/31/2028
U01 DK119094 (Gurtner/Zhou) $2,559,641
NIH-NIDDK via University of Arizona
The University of Arizona Wound Care Center Clinical Research Unit

Zhou, Wei (Site-PI) 09/17/2024-08/31/2029
1U24HL169563-01, Ambrosius, Walter (PI) $738,914
NIH-NHLBI
2/2 Improving Mobility After Revascularization in Peripheral Artery Disease

Ebenezer Yamoah (PI) 07/01/25-06/31/30
NIH, NIDCD $424,999.00
Cochlear neuron functions and diseases

Robert Alexander (Collaborator) 07/2021-06/2027
Eli Lilly and Company $4,116,286
TRAILBLAZER-ALZ3

Robert Alexander (Collaborator) 03/01/2023-Present
F. Hoffmann-La Roche Ltd. $496,276
A single-center, adaptive, repeated dose, parallel Phase I study to investigate in autosomal-dominant Alzheimer's disease the pharmacodynamics of RO7269162 following oral administration in presymptomatic PSEN1 E280A mutation carriers and in non-carriers from the same kindred (BP44161)

Robert Alexander (Co-I) 08/2022-01/2027
NIH/NIA via Institute for Molecular Medicine $109,978
(Agadjanyan/Schneider/Sultzer)

Safety/Tolerability/Immunogenicity of first-in-human Aβ DNA vaccine, AV-1959D Phase 1 trials in early-stage AD subjects: based on IND18953 cleared by FDA

Robert Alexander (PI) 09/2018-11/2025
NIH/NIA R01AG058468 $32,005,950
(Reiman/Aisen/Alexander/Johnson/Langbaum/Sperling)
API A4 Alzheimer's Prevention Trial

Robert Alexander (PI) 09/01/2024-08/31/2029
NIH/NIA R01AG086363 $74,457,897
(Alexander/Langbaum/Quiroz/Reiman)
Alzheimer's Prevention Initiative ADAD Colombia Trial Program

Robert Alexander (PI) 05/01/2024-04/31/2029
NOMIS Foundation $3,000,000
Advancing the Study, Treatment and Prevention of Alzheimer's Disease (AD) in Colombian PSEN1 E280A Mutation Carriers from the World's Largest Autosomal Dominant Alzheimer's Disease (ADAD) Kindred

Christine Belden (Project Co-I) 07/01/2025-06/30/2026
Arizona DHS via Arizona Alzheimer's Consortium $50,000
Returning Results to Research Participants

Claire Erickson (Project PI) 07/01/2025-06/30/2026
Arizona DHS via Arizona Alzheimer's Consortium $27,778
User testing, perceptions, understanding, and satisfaction with learning pTau-217 results

Claire Erickson (Project PI) 07/01/2025-06/30/2027
NIH/NIA P30AG072980 via Arizona State University $21,600
Arizona Alzheimer's Disease Research Center
(ADRC) -- REC Scholar

Claire Erickson (Project Co-I) 07/01/2025-06/30/2026
Arizona DHS via Arizona Alzheimer's Consortium $50,000
Returning Results to Research Participants

Jessica Langbaum (Co-I) 08/01/2025-07/31/2030
NIH/NIA via Pennsylvania State University $7,948,867
U24AG092760 (Sliwinski/Chow/Germine/Han) ($228,534 Banner Subaward)
The NIH Precision Brain Health Network: Open and Inclusive Measurement of Neuropsychological Change for AD/ADRD Primary Prevention Trials

Jessica Langbaum (PI) 09/01/2024-08/31/2029
NIH/NIA R01AG086363 $74,457,897
(Alexander/Langbaum/Quiroz/Reiman)
Alzheimer's Prevention Initiative ADAD Colombia Trial Program

Jessica Langbaum (Collaborator) 07/2021-06/2027
Eli Lilly and Company $4,116,286
TRAILBLAZER-ALZ3

Jessica Langbaum (Co-I) 09/01/2021-08/01/2028
NIH/NIA via University of Washington $145,347,642
U01AG082350 $998,440 Banner Subaward
(Johnson, Biber, Dickerson, Foroud, Kukull, Mormino, Okonkwo, Rivera-Mindt, Rabinovici, Wolk)
ADRC Consortium for Clarity in ADRD Research Through Imaging (CLARiTI)

Jessica Langbaum (PI, Core Co-Leader) 09/01/2021-06/30/2027
NIH/NIA via Arizona State University P30AG072980 $15,077,717
Arizona Alzheimer's Disease Research Center

Jessica Langbaum (PI) 09/01/2018-11/30/2025
NIH/NIA R01AG058468 $32,005,950
(Reiman/Aisen/Alexander/Johnson/Langbaum/Sperling)
API A4 Alzheimer's Prevention Trial

Jessica Langbaum (PI) 09/01/2019-06/30/2026
NIH/NIA R01 AG063954 (Langbaum/Bleakley) $8,793,374
Establishing the science behind Alzheimer's recruitment registries: opportunities for increasing diversity and accelerating enrollment into trials

Jessica Langbaum (PI) 07/01/2020-03/31/2027
NIH/NIA R01AG069453 $27,473,070
(Reiman/Woodruff/Su/Langbaum)
APOE in the Predisposition to, Protection from and Prevention of Alzheimer's Disease

Jessica Langbaum (PI) 08/01/2021-07/31/2026
NIH/NIA R33AG070604 (Langbaum) $3,941,399
Optimizing Research Infrastructure of Registries to Accelerate Participant Recruitment into Alzheimer's Focused Studies

Jessica Langbaum (Project PI) 07/01/2025-06/30/2026
Arizona DHS via Arizona Alzheimer's Consortium $51,444
Alzheimer's Prevention Registry and its GeneMatch Program

Jessica Langbaum (Project PI) 07/01/2025-06/30/2026
Arizona DHS via Arizona Alzheimer's Consortium $50,000
Returning Results to Research Participants

Jessica Langbaum (Collaborator) 03/01/2023-Present
F. Hoffmann-La Roche Ltd. $496,276
A single-center, adaptive, repeated dose, parallel Phase I study to investigate in autosomal-dominant Alzheimer's disease the pharmacodynamics of RO7269162 following oral administration in presymptomatic PSEN1 E280A mutation carriers and in non-carriers from the same kindred (BP44161)

Jessica Langbaum (Co-I) 03/01/2021-02/28/2026
NIH/NIA via University of Wisconsin-Madison $264,852
R01AG070883 (Bendlin/Kind)
The Neighborhoods Study: Contextual Disadvantage and Alzheimer's Disease and Related Dementias

Jessica Langbaum (Co-I) 05/01/2024-04/30/2029
NOMIS Foundation (Reiman, Langbaum, Alexander) $3,000,000
Advancing the Study, Treatment and Prevention of Alzheimer's Disease (AD) in Colombian PSEN1 E280A Mutation Carriers from the World's Largest Autosomal Dominant Alzheimer's Disease (ADAD) Kindred

Jessica Langbaum (Co-I) 07/01/2021-05/31/2026
NIH U24AG072122 via University of Washington $128,560
National Alzheimer's Coordinating Center (NACC)

Michael Malek-Ahmadi (Co-I) 09/01/2021-06/30/2027
NIH/NIA via Arizona State University $15,077,717
P30AG072980 (Langbaum)
Arizona Alzheimer's Disease Research Center – Data Management & Statistics Core

Michael Malek-Ahmadi (PI) 07/01/2025-06/30/2026
State of Arizona DHS via Arizona Alzheimer's Consortium $100,000
Statistical and Image Analysis Resource for Alzheimer's Researchers Inside and Outside of Arizona

Michael Malek-Ahmadi (Site PI) 04/01/2023-03/31/2028
NIH via Dignity Health RF1AG081286 (Perez) $148,485
Default Mode Network Dysfunction in Down Syndrome

Michael Malek-Ahmadi (Core Leader; Co-I) 04/01/2020-03/31/2027
NIH/NIA via Dignity Health P01AG014449 (Mufson) $793,090
Neurobiology of Mild Cognitive Impairment in the Elderly

Michael Malek-Ahmadi (Co-I) 07/01/2025-06/30/2026
State of Arizona DHS via Arizona Alzheimer's Consortium $33,333
Impact of Cholinesterase-Inhibitors on Clinical Trajectories, Milestones and Mortality in Autopsy-Supported Alzheimer's Disease

Michael Malek-Ahmadi (Co-I) 07/01/2025-06/30/2026
State of Arizona DHS via Arizona Alzheimer's Consortium $27,778
Development, Validation and Implementation of Cognitive and Clinical Composites for the Arizona Study of Aging and Neurodegenerative Disorders/BBDP

Michael Malek-Ahmadi (Project Co-I) 07/01/2025-06/30/2026
State of Arizona DHS via Arizona Alzheimer's Consortium $197,778
Clinical and Biological Characterization of The Longevity Cohort Study: Global Staging and Biospecimen Banking

Michael Malek-Ahmadi (Site PI) 08/01/2025-07/31/2028
NIH/NINDS via Southern Illinois University $42,785
Educating Biomedical Researchers on Scientific Design, Strengthening Inferences, and Interpretation

Michael Malek-Ahmadi (Site PI) 09/15/2025-09/14/2029
NIH/NIA via Arizona State University $62,245

Developing a performance-based measure of daily function for screening Hispanic/Latino older adults for Alzheimer's disease risk

Lori Nisson (PI) 07/01/2025-06/30/2026
State of Arizona DHS via Arizona Alzheimer's Consortium $66,667
Native American Outreach, Recruitment, and Retention Program

Jeremy Pruzin (Co-I) 09/30/2025-06/30/2030
NIH via University of Utah $17,747,832
Examining Effects and Neuroprotective Mechanisms of Intensive BP control by Aβ Status on mild cognitive impairment and Dementia: Enhancing SPRINT with Longitudinal AD/ADRD Plasma Biomarkers

Jeremy Pruzin (Co-I) 07/01/2023-03/31/2026
NIH via Arizona State University R01AG076566 (Yu) $323,271
Precision Medicine in Alzheimer's Disease: A SMART Trial of Adaptive Exercises and their Mechanisms of Action Using AT(N) Biomarkers to Optimize Aerobic Fitness

Eric Reiman (PI) 10/01/2020-03/31/2027
NIH/NIA R01 AG069453 $27,473,070
(Reiman/Su/Langbaum/Woodruff)
APOE in the Predisposition to, Protection from and Prevention of Alzheimer's Disease

Eric Reiman (Co-I) 05/01/2022-03/31/2027
NIH via University of Southern California $1,015,500
P01AG052350 (Toga)
Vascular Contributions to Dementia and Genetic Risk Factors for Alzheimer's Disease

Eric Reiman (Co-I) 03/01/2020-06/30/2026
Alzheimer's Association $482,898
via University of Southern California
VCID-17-209279 (Toga)
Vascular Contributions to Dementia and Amyloid and Tau Lesions in APOE4 Carriers (VCID)

Eric Reiman (Co-I) 03/01/2021-02/28/2026
NIH/NIA via University of Wisconsin-Madison $264,852
R01AG070883 (Bendlin/Kind)
The Neighborhoods Study: Contextual Disadvantage and Alzheimer's Disease and Related Dementias

Eric Reiman (Co-I) 08/01/2022-07/30/2027
NIH/NIA RF1AG0733424 (Su) $3,695,313
Tracer harmonization for amyloid and tau PET imaging using statistical and deep learning techniques

Eric Reiman (Co-I) 05/01/2021-10/31/2025
NIH/NIA via University of Arizona $347,747
OT2HL161847 (Nikolich-Zugich)
Researching COVID To Enhance Recovery (RECOVER) Initiative

Eric Reiman (Collaborator) 07/01/2021-06/30/2027
Eli Lilly and Company $4,116,286
TRAILBLAZER-ALZ3

Eric Reiman (Collaborator) 03/01/2023-Present
F. Hoffmann-La Roche Ltd. $496,276
A single-center, adaptive, repeated dose, parallel Phase I study to investigate in autosomal-dominant Alzheimer's disease the pharmacodynamics of RO7269162 following oral administration in presymptomatic PSEN1 E280A mutation carriers and in non-carriers from the same kindred (BP44161)

Eric Reiman (Co-PI) 09/01/2020-12/31/2025
Gates Ventures via Banner Alzheimer's Foundation $3,085,720
Resources for the Diagnostic and Prognostic Validation of Blood-Based Biomarkers of Alzheimer's Disease, Parkinson's Disease and Related Disorders

Eric Reiman (PI) 09/01/2024-08/31/2029
NIH/NIA $74,457,897
R01AG086363 (Alexander/Langbaum/Quiroz/Reiman)
Alzheimer's Prevention Initiative ADAD Colombia Trial Program

Eric Reiman (PI) 09/01/2018-11/30/2025
NIH/NIA $32,005,950
R01AG058468 (Reiman/Aisen/Alexander/Johnson/ Langbaum/Sperling)
API / A4 Alzheimer's Prevention Trial

Eric Reiman (PI) 09/01/2024-08/31/2026
NIH via University of Arizona $906,472
OT2 OD 037642 (Moreno/Radovick/Reiman/Theodorou)
University of Arizona-Banner Health Mountain Consortium

Eric Reiman (PI) 05/01/2024-04/30/2029
NOMIS Foundation $3,000,000
Advancing the Study, Treatment and Prevention of Alzheimer's Disease (AD) in Colombian PSEN1 E280A Mutation Carriers from the World's Largest Autosomal Dominant Alzheimer's Disease (ADAD) Kindred

Eric Reiman (PI) 01/01/2026-12/31/2026
NOMIS Foundation (Reiman) $800,000
A Public Resource of RNA Sequencing Data from Different Human Brain Cells and Regions, Associated Whole Genome Sequencing, Longitudinal Clinical, and Neuropathological Data, and Cell-Specific Multi-Scale Networks in the Alzheimer's and Aging Brain

Eric Reiman (Co-I) 09/01/2021-06/30/2027
NIH/NIA via Arizona State University $15,077,717
P30AG072980 (Langbaum)
Arizona Alzheimer's Disease Research Center

Eric Reiman (PI) 08//01/2024-7/31/2029
NIH/NIA via Boston University $957,430
R01NS139383 (Alosco/Rabinovici/Reiman/Stern)

Risk and Resilience, Clinical presentation, and Biomarker Profiles of Chronic Traumatic Encephalopathy and Related Dementias: The DIAGNOSE CTE Research Project II

Eric Reiman (Co-I) 09/01/2025-06/30/2030
NIH/NIA via University of Utah (Pruzin) $17,747,832
Examining Effects and Neuroprotective Mechanisms of Intensive BP control by Aβ Status on mild cognitive impairment and Dementia: Enhancing SPRINT with Longitudinal AD/ADRD Plasma Biomarkers

Yi Su (Co-I) 09/01/2024-08/31/2029
R01AG086363 (Alexander/Langbaum/Quiroz/Reiman) $74,457,897
Alzheimer's Prevention Initiative ADAD Colombia Trial Program

Yi Su (Co-I) 09/01/2018-11/30/2025
R01AG058468 $32,005,950
(Reiman/Aisen/Alexander/Johnson/ Langbaum/Sperling)
API / A4 Alzheimer's Prevention Trial

Yi Su (Co-I) 09/01/2024-08/31/2028
NIH U01AG082350 via University of Washington $998,440
(Johnson/Sterling)
ADRC Consortium for Clarity in ADRD Research Through Imaging (CLARiTI)

Yi Su (PI) 07/01/2025-06/30/2026
Arizona DHS via Arizona Alzheimer's Consortium $45,000
Automating Centralized Data Management Program for Arizona's Alzheimer's Disease and Related Studies

Yi Su (PI) 07/01/2025-06/30/2026
Arizona DHS via Arizona Alzheimer's Consortium $177,778
Advanced Imaging Data Analysis and ML/AI in Alzheimer's Researcher

Yi Su (Co-PI) 07/01/2025-06/30/2026
Arizona DHS via Arizona Alzheimer's Consortium $100,000
Statistical and Image Analysis Resource for Alzheimer's Researcher's Inside and Outside of Arizona

Yi Su (Co-PI) 09/01/2025-06/30/2030
NIH/NIA via University of Utah $17,747,832
Examining Effects and Neuroprotective Mechanisms of Intensive BP control by Aβ Status on mild cognitive impairment and Dementia: Enhancing SPRINT with Longitudinal AD/ADRD Plasma Biomarkers

Yi Su (Co-I) 04/01/2023-03/31/2028
NIH via Arizona State University R01AG076566 (Yu) $323,271
Precision Medicine in Alzheimer's Disease: A SMART Trial of Adaptive Exercises and their Mechanisms of Action Using AT(N) Biomarkers to Optimize Aerobic Fitness

Yi Su (Core Leader, Co-Leader) 09/01/2021-06/30/2027
NIH/NIA via Arizona State University $15,077,717
P30AG072980 (Langbaum)

Arizona Alzheimer's Disease Research Center – DMSC, Biomarker Core

Yi Su (PI) 08/01/2022-07/30/2027
NIH/NIA RF1AG0733424 $3,695,313
Tracer harmonization for amyloid and tau PET imaging using statistical and deep learning techniques

Yi Su (PI) 09/30/2020-03/31/2027
NIH/NIA R01 AG069453 $27,473,070
(Reiman/Su/Langbaum/Woodruff)
APOE in the Predisposition to, Protection from and Prevention of Alzheimer's Disease

Yi Su (Co-I) 08/15/2024-07/31/2029
NIH/NIA via Boston University $957,430
R01NS139383 (Alosco/Rabinovici/Reiman/Stern)
Risk and Resilience, Clinical presentation, and Biomarker Profiles of Chronic Traumatic Encephalopathy and Related Dementias: The DIAGNOSE CTE Research Project II

Pierre Tariot (Co-I) 09/01/2018-11/30/2025
NIH/NIA $32,005,950
R01AG058468 (Reiman/Aisen/Alexander/Johnson/Langbaum/Sperling)
API A4 Alzheimer's Prevention Trial

Pierre Tariot (Co-I) 09/01/2023-08/31/2028
NIH via University of Southern California $1,770,000
U24AG057437 (Aisen)
Alzheimer's Clinical Trial Consortium (ACTC)

Pierre Tariot (Co-I) 09/01/2024-08/31/2029
NIH/NIA $74,457,897
R01AG086363 (Alexander/Langbaum/Quiroz/Reiman)
Alzheimer's Prevention Initiative ADAD Colombia Trial Program

Po-Heng Tsai (Site PI) 07/01/2021-06/30/2027
NIH/NIA via Arizona State University $15,077,717
P30AG072980 (Langbaum)
Arizona Alzheimer's Disease Research Center – Clinical Core

Po-Heng Tsai (PI) 09/01/2023-08/31/2028
NIH via University of Southern California $1,770,000
U24AG057437 (Aisen)
Alzheimer's Clinical Trial Consortium (ACTC)

Nicholas Ashton (Co-I) 09/01/2021-06/30/2026
NIH/NIA P30AG072980 (Langbaum) $15,077,717
Arizona Alzheimer's Disease Research Center

Nicholas Ashton (PI) 07/01/2026-06/30/2029
Michael J Fox Foundation $6,000,000
Aligning Science Across Parkinson's (ASAP)

Clinical Deployment to PD-BUILD: Biomarker Utilization, Innovation, and Laboratory-to-Deployment

Nicholas Ashton (Co-I) 09/01/2025-08/30/2030
NIH/NIA U54NS092091 via University of Miami $136,786
University of Pennsylvania (Benatar)
Clinical Research in ALS and Related Disorders for Therapeutic Development (CReATe)

Nicholas Ashton (Co-I) 09/01/2020-03/31/2027
NIH/NIA 5R01AG069453-04 $28,351,326
(Reiman/Langbaum/Su/Woodruff)
APOE in the Predisposition to, Protection from and Prevention of Alzheimer's Disease

Nicholas Ashton (PI) 08/01/2025-07/31/2030
NIH via Penn State $228,534
THE NIH PRECISION BRAIN HEALTH NETWORK: Open and Inclusive Measurement of Neuropsychological Change for AD/ADRD Primary Prevention Trials

Nicholas Ashton (Co-I) 08/01/2024-7/30/2029
NIH/NIA via Boston University $957,430
R01NS139383 (Alosco/Rabinovici/Reiman/Stern)
Risk and Resilience, Clinical presentation, and Biomarker Profiles of Chronic Traumatic Encephalopathy and Related Dementias: The DIAGNOSE CTE Research Project II

Nicholas Ashton (PI) 07/01/2025-06/30/2026
C-Path Institute via Arizona Alzheimer's Consortium $97,488
CTR057001
Longitudinal head-to-head of high-precision plasma p-tau217 assays to better determine disease progression

Nicholas Ashton (PI) 07/01/2025-06/30/2026
AZ DHS via Arizona Alzheimer's Consortium $160,000
CTR057001
A Resource of Alzheimer's Disease Fluid Biomarker Expertise and Assays for Researchers in the Arizona Alzheimer's Consortium

Nicholas Ashton (PI) 4/01/2025-03/15/2027
The Alzheimer's Drug Discovery Foundation $322,194
RT-202409-2027020
Developing immunoassay for MTBR-243 to diagnose Alzheimer's disease

Nicholas Ashton (PI) 07/01/2025-06/30/2028
TargetALS Foundation $416,823
BM-2025-C1-L2
Assays development for HDGFL2 and phosphorylated TDP-34

Nicholas Ashton (PI) 07/01/2025-06/30/2026
AZ DHS via Arizona Alzheimer's Consortium $55,555
CTR057001
DROP-AD: A capillary blood test for Alzheimer's disease pathology

Nicholas Ashton (Co-I) 07/01/2025-06/30/2030
NIH via University of Utah (Pruzin) $4,573,808
R01AG096179
Examining Effects and Neuroprotective Mechanisms of Intensive BP control by Aβ Status on mild cognitive impairment and Dementia: Enhancing SPRINT with Longitudinal AD/ADRD Plasma Biomarkers

Nicholas Ashton (Co-I) 07/01/2025-06/30/2027
AZ DHS via Arizona Alzheimer's Consortium (Choudhury) $271,734
CTR057001
Integrating Proteomics and AI in Lewy Body Disease Biomarker Discovery

Nicholas Ashton (Co-I) 09/01/2024-08/31/2029
NIH/NIA $74,457,897
R01AG086363 (Alexander/Langbaum/Quiroz/Reiman)
Alzheimer's Prevention Initiative ADAD Colombia Trial Program

Nicholas Ashton (Co-I) 01/01/2025-01/01/2027
Michael J Fox Foundation (Beach) $271,734
MJFF-025460
Synuclein CSF SAA and Biofluids AD Biomarkers within the Arizona Study of Aging and Neurodegenerative Disorders

Alireza Atri (Core Co-Lead, Core Lead, Co-I; Site PI) 07/01/2021-06/30/2027
NIH via Arizona State University $15,077,717
P30AG072980 (Langbaum)
Arizona Alzheimer's Disease Research Center-Admin Core, Clinical Core, Biomarker Core

Alireza Atri (Co-I) 09/01/2024-08/31/2028
NIH U01AG082350 $998,440
via University of Washington (Johnson/Sterling)
ADRC Consortium for Clarity in ADRD Research Through Imaging (CLARiTI)

Alireza Atri (Co-PI) 09/01/2022-09/01/2028
Foundation for the National Institutes of Health (Finnema) ~$3,000,000
Pre- competitive Analytical Validation of SV2A PET as a Biomarker of Synaptic Density (From Imaging to Autopsy)

Alireza Atri (Co-PI) 09/01/2020-12/31/2025
Gates Ventures $3,085,720
via Banner Alzheimer's Foundation (Reiman)
Resources for the Diagnostic and Prognostic Validation of Blood-Based Biomarkers of Alzheimer's Disease, Parkinson's Disease and Related Disorders

Alireza Atri (Co-I) 09/01/2024-08/31/2029
NIH/NIA $74,457,897
R01AG086363 (Alexander/Langbaum/Quiroz/Reiman)
Alzheimer's Prevention Initiative ADAD Colombia Trial Program

Alireza Atri (Site PI) 09/15/2023-08/31/2028
NIH via University of Southern California $2,019,288

U24AG057437 (Aisen)
Alzheimer's Clinical Trial Consortium (ACTC)

Alireza Atri (Co-I) 03/01/2021-02/28/2026
NIH/NIA via University of Wisconsin-Madison $264,852
R01AG070883 (Bendlin/Kind)
The Neighborhoods Study: Contextual Disadvantage and Alzheimer's Disease and Related Dementias

Alireza Atri (Co-I) 06/01/2022- 05/31/2026
NIH via Indiana University U01AG057195 (Apostolova) $168,927
Early Onset AD Consortium-the LEAD Study (LEADS) Social Worker Funds

Alireza Atri (Site PI) 11/01/2021-10/31/2026
Washington University St. Louis NCT01760005 (Bateman) $370,945
DIAN-TU Gantenerumab Open Label Extension (OLE) Trial Project Arm Leader

Alireza Atri (Project PI) 07/01/2025-06/30/2026
Arizona DHS via Arizona Alzheimer's Consortium (Atri) $197,778
Clinical Phenotyping and Biological Characterization of The Longevity Cohort Study: Global Staging and Biospecimen Banking

Alireza Atri (Project PI) 07/01/2025-06/30/2026
Arizona DHS via Arizona Alzheimer's Consortium (Atri) $27,778
Development, Validation and Implementation of Cognitive and Clinical Composites for the Arizona Study of Aging and Neurodegenerative Disorders/BBDP

Alireza Atri (Project Co-I) 07/01/2025-06/30/2026
Arizona Alzheimer's Consortium $44,444
via Arizona DHS (Choudhury)
Trajectories of clinical symptoms and associations with pathology in Lewy body spectrum disorders

Alireza Atri (Co-I) 01/01/2025-01/01/2027
MJFF-025460 (Beach) $647,836
Synuclein CSF SAA and Biofluids AD Biomarkers within the Arizona Study of Aging and Neurodegenerative Disorders

Thomas Beach (Co-I) 09/01/2024-08/31/2026
MJFF via Yale ASAP-000301(Scherzer) $155.143
Parkinson5D: deconstructing proximal disease mechanisms across cells, space, and progression

Thomas Beach (Co-I) 07/01/2021-06/30/2026
NIH/NIA via ASU P30AG072980 (Langbaum) $4,984,211
Arizona Alzheimer's Disease Research Center-Biomarker Core

Thomas Beach (Co-I) 03/01/2021-02/28/2026
NIH/NIA via University of Wisconsin-Madison $264,852
R01AG070883 (Kind)

The Neighborhoods Study: Contextual Disadvantage and Alzheimer's Disease and Related Dementias

Thomas Beach (Co-I) 02/01/2024-01/31/2028
NIH via BU R01HL171499 (Mizgerd) $96,700
Fibrin in the Infected Lung

Thomas Beach (Consultant) 05/17/2021-05/16/2026
Phoenix VA Health Care System $60,000
2I01BX003767-05 (Migrino)
Discovering novel mechanisms for aging-related dementia: probing medin and abeta vasculopathy

Thomas Beach (Core Leader) 09/05/2021-06/30/2026
NIH/NIA via ASU P30AG072980 (Langbaum) $1,636,000
Arizona Alzheimer's Disease Research Center-Neuropathology Core

Thomas Beach (PI) 08/01/2021-08/31/2028
NIH/NINDS R01NS118669 (Beach) $3,195,450
Blinded Comparison of Different Alpha-Synuclein Seeding Assays as Cutaneous Biomarkers of Lewy Body Dementias

Thomas Beach (PI) 06/23/2016-12/31/2025
MJFF-020674 (Beach) $829,489
Systemic Synuclein Sampling Study

Thomas Beach (Site PI) 08/15/2021-01/31/2027
NIH via UCSF Gladstone P01AG073082 (Mucke) $200,575
Decoding the Multifactorial Etiology of Neural Network Dysfunction in Alzheimer's Disease

Thomas Beach (Site PI) 08/15/2021-4/30/2026
NIH via UCSD R01AG074221 (Sundermann) $128,786
Sex Differences in the Clinical Expression of Alzheimer's Disease Neuropathology and Their Underlying Biological Mechanisms

Thomas Beach (Site PI) 08/01/2024-07/30/2026
NIH via Virtici LLC 1R43NS139747-01 $70,518
A Novel Blood Test for Early Diagnosis of Frontotemporal Lobar Degeneration

Thomas Beach (Site PI) 12/01/2021-11/30/2026
NIH via Binghamton University R01NS122226 (Bishop) $54,597
Interrogating maladaptive serotonin raphe-striatal plasticity in L-DOPA-induced dyskinesia

Thomas Beach (Site PI) 04/01/2022-03/31/2027
NIH via Stanford University R01AI162850 (Mizgerd) $203,196
Pulmonary Pathophysiology Sub-Phenotypes of Pneumonia

Thomas Beach (Site PI) 09/01/2021-06/30/2026
NIH via Case Western University R01AG067607 (Kraus) $27,714
Skin biomarkers for diagnosing and characterizing AD and ADRD

Thomas Beach (Site-PI) 04/01/2023-03/31/2028
NIH via UCSD R01AG079280-01 (Frank) $143,353
Joint Estimation Diffusion Imaging (JEDI) for Improved Tissue Characterization and Neural Connectivity in Aging and Alzheimer's Disease

Thomas Beach (Site-PI) 12/01/2022-11/30/2027
NIH via LSU 5R01CA263494-04 (Wu) $68,713
Uncovering causal protein markers to characterize prostate cancer etiology and improve risk prediction in Africans and Europeans

Thomas Beach (Co-PI) 01/01/2025-01/01/2027
MJFF-025460 $647,836
Synuclein CSF SAA and Biofluids AD Biomarkers within the Arizona Study of Aging and Neurodegenerative Disorders

Thomas Beach (Co-I) 07/01/2024-06/30/2029
NIH via Stanford University 1R01AG088656-01 (Jaiswal) $220,362
Uncovering mechanisms of protection from Alzheimer's disease in CHIP using human cohorts and biosamples

Thomas Beach (Co-PI) 02/01/2025-02/01/2027
MJFF-026548 $276,569
Alphasynuclein Post-Translational Modification Quantification Program

Thomas Beach (Site PI) 09/01/2025-08/31/2029
NIH via LSU 1U01CA293883-01 (Wu) $117,002
Uncovering Causal Protein Markers to Characterize Pancreatic Cancer Etiology and Improve Risk Prediction

Thomas Beach (Site PI) 06/01/2025-03/31/2030
NIH via St Jude's 1R01AG092468-01 (Peng) $194,875
Proteogenomics of Splicing Proteinopathies in Neurodegeneration

Thomas Beach (Co-I) 01/01/2026-12/31/2026
Nomis Foundation (Reiman) $800,000
A Public Resource of RNA Sequencing Data from Different Human Brain Cells and Regions, Associated Whole Genome Sequencing, Longitudinal Clinical, and Neuropathological Data, and Cell-Specific Multi-Scale Networks in the Alzheimer's and Aging Brain

Thomas Beach (Co-I) 06/01/2026-01/31/2028
ASAP MJFF via UCL (Jaunmuktane) $324,033
Multi-Brain Bank Neurodegenerative Disease Tissue Digitization

Thomas Beach (Co-I) 06/01/2026-05/31/2029
ASAP CRN via Stanford University (Soto) $741,850
Understanding alpha-synuclein seeding: Identification of cellular factors influencing seeding and structural and biological characterization of the SAA products

Thomas Beach (Site PI) 08/01/2025-07/31/2027
NIH via UCLA (Bitan) $49,532
A novel diagnostic assay for rare parkinsonian tauopathies

Thomas Beach (Site PI) 04/01/2026-03/31/2027
NIH via UF (Valliancourt) $100,000
Web-based Automated Imaging Differentiation of Parkinsonism

Parichita Choudhury (PI) 01/01/2024-12/31/2027
Lewy Body Dementia Association (Choudhury/Chiu) $12,500/year (renewable annually)
Research Center of Excellence Program Award

Parichita Choudhury (Co-I, Core Co-Leader) 07/01/2021-06/30/2027
NIH via Arizona State University $15,077,717
P30AG072980 (Langbaum)
Arizona Alzheimer's Disease Research Center

Parichita Choudhury (Project PI, Clinical Core Co-Lead) 01/01/2023-06/30/2026
NIH via Arizona State University $26,666
P30AG072980 (Langbaum)
Arizona Alzheimer's Disease Research Center – REC Fellowship

Parichita Choudhury (Co-I) 09/15/2023-08/31/2028
NIH via University of Southern California $2,019,288
U24AG057437 (Aisen)
Alzheimer's Clinical Trial Consortium (ACTC)

Parichita Choudhury (Co-I) 09/01/2024-08/31/2029
NIH/NIA $74,457,897
R01AG086363 (Alexander/Langbaum/Quiroz/Reiman)
Alzheimer's Prevention Initiative ADAD Colombia Trial Program

Parichita Choudhury (Project PI) 07/01/2025-06/30/2026
Arizona Alzheimer's Consortium $44,444
via Arizona DHS (Choudhury)
Clinical trajectories and associations with pathology in Lewy body spectrum disorders

Parichita Choudhury (Co-I) 07/01/2025-06/30/2026
Arizona Alzheimer's Consortium via Arizona DHS (Atri) $27,778
Development, Validation and Implementation of Cognitive and Clinical Composites for the Arizona Study of Aging and Neurodegenerative Disorders/BBDP

Parichita Choudhury (Co-I) 01/01/2025-01/01/2027
MJFF-025460 (Beach) $647,836
Synuclein CSF SAA and Biofluids AD Biomarkers within the Arizona Study of Aging and Neurodegenerative Disorders

Geidy Serrano (Co-I) 01/01/2026-12/31/2026
Nomis Foundation (Reiman) $800,000
A Public Resource of RNA Sequencing Data from Different Human Brain Cells and Regions, Associated Whole Genome Sequencing, Longitudinal Clinical, and Neuropathological Data, and Cell-Specific Multi-Scale Networks in the Alzheimer's and Aging Brain

Geidy Serrano (Co-I) 08/15/2021-08/31/2026
NIH/NINDS R01NS118669-01 (Beach) $3,195,450
Blinded Comparison of Different Alpha-Synuclein Seeding Assays as Cutaneous Biomarkers of Lewy Body Dementias

Geidy Serrano (Co-I) 09/05/2021-06/30/2026
NIH/NIA via ASU P30AG072980 (Langbaum) $4,984,211
Arizona Alzheimer's Disease Research Center-Biomarker Core

Geidy Serrano (Core Co-Leader; Co-I) 09/05/2021-06/30/2026
NIH/NIA via ASU P30AG072980 (Langbaum) $1,636,000
Arizona Alzheimer's Disease Research Center-Neuropathology Core

Geidy Serrano (Project PI) 07/01/2025-06/30/2026
Arizona DHS via Arizona Alzheimer's Consortium $257,000
Patient-based live cell banking for translational research

Geidy Serrano (Site PI) 07/01/2025-06/30/2026
Arizona Alzheimer's Consortium via ASU (Mastroeni) $7,965
Quantifying Micro- and Nanoplastics in the Aging Brain: Associations with Alzheimer's Disease Pathology and Socioeconomic Disadvantage

Geidy Serrano (Co-I) 07/01/2024-06/30/2025
Arizona Alzheimer's Research Consortium (Atri) $165,000
AAC: Enhancing Clinical and Biological Characterization of The Longevity Cohort Study: Global Staging and Biospecimen Banking

Geidy Serrano (Site-PI) 04/01/2021-03/31/2026
NIH/University of Arizona R01AG072643 (Barnes) $40,875
NPTX2: Preserving memory circuits in normative aging and Alzheimer's Disease

Geidy Serrano (Site-PI) 12/01/2023-11/30/2028
NIH via UC Irvine R01AG077700 (Mukherjee) $106,596
Novel Tau-Targeted Radiohalogenated Agents for Alzheimer's Disease

Geidy Serrano (Site-PI) 09/01/2024-08/31/2027
NIH via UCLA RF1NS139972 $109,931
Defining the molecular spectrum of white matter vascular lesions

Geidy Serrano (Co-PI) 01/01/2025-01/01/2027
MJFF-025460 $647,836
Synuclein CSF SAA and Biofluids AD Biomarkers within the Arizona Study of Aging and Neurodegenerative Disorders

Geidy Serrano (Co-I) 02/01/2025-02/01/2027
MJFF-026548 (Beach) $276,569
Alphasynuclein Post-Translational Modification Quantification Program

Geidy Serrano (Co-I) 07/01/2024-06/30/2029
NIH via Stanford University 1R01AG088656-01 (Jaiswal) $220,362

Uncovering mechanisms of protection from Alzheimer's disease in CHIP using human cohorts and biosamples

Geidy Serrano (Site PI) 07/01/2026-06/30/2029
ASAP-027762 via DZNE $940,338
Development and Validation of Labeled Antibodies Against Mitochondrial and Oxidative Stress-Related Targets for Parkinson’s Disease Research

Geidy Serrano (Site-PI) 06/01/2026-01/31/2028
ASAP MJFF via UCL(Jaunmuktane) $324,033
Multi-Brain Bank Neurodegenerative Disease Tissue Digitization

Geidy Serrano (Co-I) 09/01/2024-08/31/2026
ASAP/MJFF via Yale ASAP-000301 (Scherzer) $155,143
Parkinson5D: deconstructing proximal disease mechanisms across cells, space, and progression (Extension)

Geidy Serrano (Site PI) 07/01/2026-06/30/2029
ASAP-027762 via DZNE $940,338
Development and Validation of Labeled Antibodies Against Mitochondrial and Oxidative Stress-Related Targets for Parkinson’s Disease Research

Madeline Andrews 2/1/2024-1/31/2027
AARG-NTF-23-1142728 $200,000
Alzheimer’s Association
Interrogating metabolic dysregulation in neurodegeneration using organoids

Madeline Andrews, PI 1/4/2023-1/3/2027
RFGA2022-010-16 $225,000
MPO FY23 - 942 / MPO FY25-1599
Arizona Biomedical Research Centre (ABRC)
Metabolic regulation of human cortical development & disease

Madeline Andrews 7/1/2026-6/30/2027
Arizona State University Foundation (ASUF) $50,000
Women and Philanthropy
Innovating human cell models to discover drivers of Alzheimer’s Disease

Madeline Andrews, Ruchira Jha 07/1/2026-16/30/2031
FP00046389 HHS: National Institutes of Health $1,360,646.00
Subaward of Dignity Health - St. Joseph's Hospital - Barrow Neurological Institute (BNI)
Molecularly Deconstructing Sexual Dimorphism in Early Brain Injury Post Aneurysmal Subarachnoid Hemorrhage: Leveraging Human Brain Organoids and Patient Biofluids

PI: Heather Bimonte-Nelson 9/01/18 - 3/1/25
NIH R01 Grant, R01AG028084
Variations in Hormones During Menopause: Effects on Cognitive and Brain Aging

PI: Sarah Stabenfeldt (ASU, Biomedical Engineering) 9/1/2020 - 8/31/2025
Co-Investigator: Heather Bimonte-Nelson
NIH R01 Grant, R01NS116657

Exploiting Sex-dependent Brain Injury Response for Nanoparticle Therapeutics

PI: Cassandra Gipson-Reichardt (University of Kentucky) 9/30/2022 - 8/31/2024
Co-Investigator: Heather Bimonte-Nelson
NIH R21 Grant, R21DA055879
Contributions of Progestins Independently and Interactively with Contraceptive Estrogen to Nicotine Use

PI: Reiman 9/5/2021 - 6/30/2026
NIH P30 AG072980
Arizona Alzheimer's Disease Research Center
Role: Research Education Core Leader

PI: Carol Barnes, Paul Coleman, Eric Reiman 5/01/2022 - 4/30/2027
Associate Directors: Heather Bimonte-Nelson, Matthew Huentelman
NIH Postdoctoral T32 Training Grant, NIA T32AG044402
Postdoctoral Training, Neurobiology of Aging and Alzheimer's Disease.

PI: Heather Bimonte-Nelson 2025
Seed Funding, ASU Institute for Social Science Research
Menopause and Estrogenic Therapy Effects on Social Memory Load

PI: Heather Bimonte-Nelson 2026
Seed Funding, ASU Institute for Social Science Research
Investigating the Interactive Effects of Female-specific Lifespan Events on Cognitive, Affective, and Brain Profiles

Co-PIs: Brafman, Kusmi, Stabenfeldt 07/01/2025-06/30/2029
NIGMS- T32GM154654 $2,131,800
RESTEP in AZ: Regenerative Engineering, Science, and Technology Education Program in Arizona

PI: Brafman 09/15/2024-08/31/2027 (NCE)
NIH-NIA, 1 R21 AG079279-01 $431,750
Dissecting the interaction between sex and APOE genotype in modulating AD risk

PI: Brafman 09/01/2024-06/30/2026
NIH-NIA, 1 R21 AG085395 $431,750
Investigating an African American-specific APOE genetic variant using hiPSC

PI: Brafman 01/01/2023-12/31/2026
Alzheimer’s Association, AARG-22- 973218 $300,000
Investigating the protective mechanisms of APOE2

Newbern J (Co-Investigator) 7/1/2025 – 6/30/2026
Bimonte-Nelson, H (Principal Investigator) $100,000
Mayo Clinic and ASU Alliance for Health Care Seed Grant
“Cognitive efficacy and brain neurochemistry profiling of a new FDA-approved nonhormonal menopausal therapy across varied menopausal conditions”

Newbern J (Co-Investigator) 04/01/2026 – 03/31/2031
FP00047011 Verpeut, J (Principal Investigator) $3,638,508
HHS-NIH R01
“Molecular analysis of perineuronal nets in cerebellar circuit plasticity”

Newbern J (Co-Investigator) 5/10/2023 – 4/30/2028
R01 AA030061 Olive, MF (PI) $1,915,852
HHS-NIH R01
“Regulation of binge like ethanol intake by arcuate POMC projection neurons”

Jui-Heng Tseng (PI) 2022-2026
AARF-22-926617 $175,000
Alzheimer’s Association (Tseng)

Jui-Heng Tseng (PI) 2025-2027
Developmental Project $120,000
Arizona Alzheimer’s Consortium

David Coon (PI): Verpeut: Sub-Project PI 7/1/2025 – 6/30/2025
FP47888 $82,000 Total Project
ADHS, Arizona Alzheimer's Consortium (AAC) FY26 Match Projects
Cerebellar pathology in Alzheimer’s disease from a translational model to humans

Jessica Verpeut (PI) Fall 2025
Institute for Social Science Research $8,000
Arizona State University (internal)
Molecular Scaffolding of the Social Cerebellum: Reprogramming Perineuronal Nets to Restore Brain Plasticity

Jessica Verpeut (PI) Spring 2026
Institute for Social Science Research $8,000 Total Project
Arizona State University (internal)
Investigating the Neural and Social Outcomes of Prenatal Opioid Exposure

Yalin Wang (PI) 9/1/2021-8/31/2025
R01EY032125 $1,559,565.00
HHS: National Institutes of Health (NIH)
Hierarchical Bayesian Analysis of Retinotopic Maps of the Human Visual Cortex with Conformal Geometry

Lepore/Linguraru (MPI), Wang (Co-I) 9/15/2021-5/31/2026
R01DE030286 $230,192.00
HHS: National Institute of Health (NIH)
Early joint cranial and brain development from fetal and pediatric imaging

Wang/Dumitrascu (MPI) 7/01/2025-12/31/2026
ASU-Mayo Seed Grant $70,000
Retinal imaging-based deep learning model to predict Alzheimer’s disease in presymptomatic stage

Pending Grants

Steven Rapcsak (Co-I) 04/01/2026 - 03/31/2031
NIH via UCSD $103,537
Personalized TMS guided by spatially resolved EEG for memory deficit mitigation in AD and MCI

Steven Rapcsak (Site PI) 09/01/2026 - 06/30/2031
NIH/NIA via Arizona State University
P30AG072980 (Langbaum)
Arizona Alzheimer's Disease Research Center

Emily Edmonds (Co-I) 04/01/2027 - 03/31/2032
NIH/NIA via UCSD $431,125
NIH (R01) Comparing neuropsychological approaches for detecting subtle cognitive decline in older adults

David Medina (PI) 07/01/26 - 6/30/2026
DOW AL250098 Pending
Targeting m6A Dysregulation in ALS via Small Molecule Approaches

Susan Racette (MPI) 09/30/2021 - 01/31/2027
R01 AG071717 (Das/Racette/Redman) $7,838,485
NIH/NIA
Legacy Effects of CALERIE, a 2-year Calorie Restriction Intervention, on Hallmarks of Healthspan and Aging

Susan Racette (Co-I) 02/15/2021 - 01/31/2030
R33 AG070455 (Huffman) $2,472,781
NIH/NIA
Enhancing the CALERIE Network to Advance Aging Biology 2.0

Susan Racette (Co-I) 08/01/2022 - 07/31/2027
R61 HL155858 (Peterson) $2,438,542
NIH/NHLBI
The Inorganic Nitrate and eXercise performance in Heart Failure (iNIX-HF): - a phase II clinical trial

Susan Racette (Co-I) 12/01/2024 - 11/30/2027
ABA (Kavouras) $2,213,993
American Beverage Association
Adequate Hydration and Health Outcomes

Susan Racette (MPI) 05/01/2023 - 12/31/2026
BNF (Geda/Racette) $400,000
Barrow Neurological Foundation
Time-Restricted Eating in Alzheimer's Disease: The TREAD Trial

Susan Racette (MPI) 07/01/2025 - 06/30/2026
AAC (Sabbagh/Racette) $111,333
Arizona Alzheimer's Consortium and Barrow

Neurological Foundation
Acute Effects of Exercise, With and Without Anti-Amyloid Therapy, on Fluid Biomarkers in Patients with Mild Cognitive Impairment

Marwan Sabbagh (PI) 07/16/2027 - 07/16/2030
Alzheimer's Association $1,000,000
Treating Mild Cognitive Impairment with Immunomodulatory Agent Lenalidomide

Rita Sattler (MPI) 07/01/26 - 06/30/31
NIH/NINDS R01 $4,241,113
Cortical astrocyte contribution to synaptic dysfunction in C9orf72 FTD/ALS

Rita Sattler (Multi-PI) 12/01/26 - 11/30/28
NIH/NINDS R21 $327,443
RNA Modifications in FTD/ALS and their Impact on TDP-43 Function and Pathology.

Diane Stephenson (PI) 07/01/2026-06/30/2027
Critical Path Institute / Banner Sun Health Research $152,000
Longitudinal and predictive modeling of CSF proteomics in PSEN1 E280A mutation carriers

Richard Caselli (Co-I) 07/01/2026-06/30/2031
P30 AG72980-06 (Langbaum) $1,066,084
National Institute of Aging
Arizona Alzheimer's Disease Research Center (ADRC) Core B

Bryan Woodruff (Co-I) 07/01/2026-06/30/2031
P30 AG72980-06 (Langbaum) $1,005,705
National Institute on Aging
Arizona Alzheimer's Disease Research Center (ADRC) Core B

Meredith Wicklund (Co-I) 07/01/2026-06/30/2031
P30 AG72980-06 (Langbaum) $1,005,705
National Institute on Aging
Arizona Alzheimer's Disease Research Center (ADRC) Core B

Dona Locke (Co-I) 07/01/2026-06/30/2031
P30 AG072980-04 (Langbaum) $1,005,705
National Institute on Aging
Arizona Alzheimer's Disease Research Center (ADRC)

Bryan Woodruff (Site PI) 12/01/2026-11/30/2031
R01 (Brafman) $46,930
National Institutes of Health (ASU Subaward)
Stabilized Programmable RNA Sensors for Amplification-Free SNP Detection at the Point of Care

Shannon Chiu (PI) 07/01/2026-06/30/2028
Career Development Award in Medical Research $100,000
(Center for Clinical and Translational Science, Mayo Clinic)
Mayo Clinic Arizona
Application of free-water imaging to identify a Lewy body disease neurodegeneration index

Joao Carvalho-de-Souza (PI) 09/01/2026-08/31/2029
NIH (NINDS) R15 REAP $552,529
Silent Kv subunits as major players in sensory neurons during chronic pain

Edward Wickstead (PI) 07/01/2026-06/30/2029
Arizona Biomedical Research Centre $225,000
Investigating the Role of the Fpr2/3-Annexin A1 Signaling Axis in Alzheimer's Disease

Edward Wickstead (PI) 07/01/2026-06/30/2028
Arizona Alzheimer’s Consortium Development Project $120,000
The Role of the FPR2-AnxA1 Signaling Axis in Alzheimer’s Disease

Edward Wickstead (PI) 07/01/2026-06/30/2029
BrightFocus Foundation $300,000
Defining the Role of FPR2-ANXA1 Signaling in Neuroinflammation Resolution and Alzheimer's Disease

Mitra Esfandiarei (Co-I) 07/01/2026-06/30/2027
NIH R15 (Subaward from Southern Illinois University) $32,427 Subaward Project
Identifying mechanisms by which maternal dietary deficiencies in choline influence ischemic stroke outcomes of offspring

Marisa Menchola (Co-I) 07/01/2026-06/30/2027
Arizona Alzheimer’s Consortium $16,545 Subaward Project
(Subaward from the University of Arizona)
Integrating Biomarker and Neuropsychological Data within Research, Memory Clinic, and Primary Care Cohorts to Optimize Diagnosis, Clinical Staging, and Treatment Selection in Alzheimer’s Disease

Mark Swanson (PI) & Nancy Bae (Co-I) 07/01/2026-06/30/2027
Arizona Alzheimer’s Consortium $9,915
Regulation of amyloidogenic and non-amyloidogenic processing of the amyloid precursor protein (APP) by gamma secretase modulators

Nancy Bae (PI) & Mark Swanson (Co-I) 07/01/2026-06/30/2027
Arizona Alzheimer’s Consortium $9,728
Identification of novel target genes of telomeric protein RAP1 that modulates amyloid production

Layla Al-Nakkash (PI) & Estela Jauregui (Co-PI) 07/01/2026-06/30/2027
Arizona Alzheimer’s Consortium $15,490
Understanding the impact of phthalates on the brain-intestinal axis

Minsub Shim (PI) & Elizabeth Hull (Co-PI) 07/01/2026-06/30/2027
Arizona Alzheimer’s Consortium $14,000
The role of cellular senescence in Alzheimer’s disease

Robert Mercer (PI) & Nicholas Haley (Co-PI) 07/01/2026-06/30/2027
Arizona Alzheimer’s Consortium $54,771
Establishment of α-syn, tau, and TDP-43 RT-QuIC assays at Midwestern University

Jonathan Frost (PI) & Kimberly Bussey (Co-I) 07/01/2026-06/30/2027
Arizona Alzheimer's Consortium $500
Salivary biomarkers for early Alzheimer disease detection: A secondary data analysis using the AAC database

Thomas Caspers (PI) 07/01/2026-06/30/2027
Kimberly Bussey (Co-I), & Mark Voigt (Co-I) $9,472
Arizona Alzheimer's Consortium
Salivary biomarker based risk profiling for early detection of Parkinson's disease in a dental clinical setting

Kathryn Lawson (PI) & Kimberly Bussey (Co-PI) 07/01/2026-06/30/2027
Arizona Alzheimer's Consortium $14,000
Investigating the Impact of Stress Hormone-Induced Astrocyte Changes on Neuronal Function

Edward Wickstead (PI) 07/01/2026-06/30/2027
Arizona Alzheimer's Consortium $24,124
The Annexin A1-FPR2 Resolution Axis: Implications for Alzheimer's Disease

Mitra Esfandiarei (Co-I) 12/01/2025-11/30/2028
NIH R15 (Subaward from Southern Illinois University) $43,190 Subaward Project
Identifying the mechanisms of maternal dietary deficiencies in choline on female and male offspring ischemic stroke outcome

J. Gregory Caporaso, PI 04/01/2027 – 03/31/2032
NIH-National Cancer Institute $4,648,587
Advancing cancer research with the QIIME 2 microbiome data science platform

Emily Cope (PI) 07/01/2026-06/30/2027
Arizona Alzheimer's Consortium Alzheimer's /AZDHS $80,000 Direct Costs
Targeting the Gut–Brain Axis in Preclinical Alzheimer's Disease Using Neuromodulatory Gut Microbes and Metabolites

J. Gregory Caporaso, Subaward PI 07/01/2026-08/31/2031
National Science Foundation, University of Utah $236,654
Immune mechanisms driving IBD-linked cholestatic disease

McCarthy, M. (Co-I) 12/01/2026-11/30/2031
NIA – R01 - PA-25-301 (Lyons, Karen) $3,916,603
Us: The role of dyadic processes in optimizing the health of lung cancer survivors and their care partners

Cerino, E. (Co-I) 12/01/2026 – 11/30/2031
NIA – R01 – PA-20-185 (Rush, Charles) $2,000,000
Linking Daily Dynamics of Social Connection to Physical and Cognitive Functioning

Matthew Huentelman (Co-I) 04/1/2027-03/31/2032
R01 (Cohen) $1,502,963
NIH via University of Pittsburgh
Alzheimer's Biomarker Consortium-Autism

Matthew Huentelman (PI) 04/01/2027-03/31/2032
R01 $8,059,280
NIH
Rural-Urban Differences in Cognitive Aging: Multimodal Predictors of Decline and Resilience

Matthew Huentelman (Co-I) 04/01/2024-03/31/2032
R01 (Gewirtz) $1,383,309
NIH via Arizona State University
Transcriptional and epigenetic mechanisms underlying opioid addiction vulnerability in male and female rats

Matthew Huentelman (Co-I) 12/01/2026-11/30/2031
R01 (Furlong) $4,072,982
NIH via University of Arizona
Agricultural Pesticide Drift and Neurodegenerative Processes in Rural and Urban Populations

Matthew Huentelman (Co-I) 12/01/2026 – 11/30/2031
R01 (Chong) $291,558
NIH via Mayo Clinic, AZ
AI-Driven risk stratification of biopsychosocial factors influencing prescription patterns, opioid exposure, and health care utilization for migraine.

Matthew Huentelman (Co-I) 12/01/2026-11/30/2028
R01 (Hefferman) $51,916
NIH via Columbia University
Carotid pulsatile damping and vascular resilience for Alzheimer's Disease

Matthew Huentelman (Co-I) 12/01/2026 -11/30/3031
R01 (Hepp) $1,335,379
NIH via Northern Arizona University
Characterizing core and aberrant protein-proein interactions driven by West Nile virus

Matthew Huentelman (Co-I) 12/01/2026 – 11/30/2031
R01 (Velazquez) $644,070
NIH via Arizona State University
Neuroprotective Mechanisms of the retinoblastoma-binding protein 7 in Alzheimer's Disease and related tauopathies

Matthew Huentelman (Co-I) 12/01/2026- 11/30/2031
R01 (Schaefer) $2,608,889
NIH via Arizona State University
On the move: Motor-based biomarkers of dementia using the MindCrowd Mobile Lab

Matthew Huentelman (PI) 12/01/2026-11/30/2031
R01 $21,755,474
NIH
Toward a Validated Intrinsic Capacity Score for Predicting Healthy Aging

Matthew Huentelman (PI) 12/01/25 -11/30/2030
R01AG098596 $4,692,786
NIH

Vascular Risk Factors and Cognitive Aging in Rural Populations

Matthew Huentelman (Co-I) 07/01/2026 – 06/30/2031
1 P30 AG072980-01 (Langbaum) Renewal Proposal $133,840
NIH via Banner Health
Arizona Alzheimer’s Disease Core Center

Matthew Huentelman (PI) 07/01/2026-06/30/2027
Arizona State Department of Health Services $89,250
via Banner Health
FY2027: Aging in rural Arizona: identification of biomarkers associated with accelerated cognitive change

Matthew Huentelman (Co-I) 04/01/2026 – 05/31/2028
R21 (Velazquez) $211,609
NIH via Arizona State University
Choline and Cognitive Health: A Translational Approach to Evaluating the Impact of Choline on Cognitive Decline, Alzheimer's Disease Biomarkers, and Tauopathies

Matthew Huentelman (Co-I) 04/01/2026 – 05/31/2031
R01 (Furlong) $409,910
PFAS Exposure, PFAS mitigation and ADRD biomarkers and cognition
NIH via University of Arizona

Matthew Huentelman (Co-I) 04/01/2026 – 03/31/2028
R21 (Wang) $28,800
NIH via Arizona State University
RetiVASC: A next-generation retinal vascular analysis system for neurodegenerative disease research

Matthew Huentelman (Co-I) 12/01/2025 – 11/30/2030
R01 (Rogalski) Renewal Proposal $276,000
NIH via University of Chicago
Cognitive SuperAging: A model to explore resilience and resistance to aging and Alzheimer’s disease

Matthew Huentelman (Co-I) 12/01/2025 – 11/30/2030
R01 (Wang) $288,000
NIH via Arizona State University
Deep Learning-based retinal imaging screening tool for preclinical Alzheimer's disease

Matthew Huentelman (Co-I) 09/15/2025 – 09/30/2029
R01 (Schaefer) $122,559
NIH via Arizona State University
Developing a performance-based measure as an equitable approach to screening Hispanic/Latino older adults for Alzheimer's disease risk

John Fryer (PI) 12/01/2026 – 11/31/2031
R01AG106015 $4,799,040
NIH
Cooperative roles of APOE and CLU in glial regulation of Alzheimer’s disease pathology

John Fryer (PI) 12/01/2026 – 11/31/2031
R01GM168831 $3,782,400
NIH
Precision, target-defined biologics for pit viper envenomation

John Fryer (PI) 04/01/2026 – 03/31/2031
R01AG100407 $4,756,937
NIH
The role of CLU in molecular pathogenesis of Alzheimer's disease

Iganzio Piras (PI) 04/1/2027 – 03/31/2032
R01 $4,877,494
NIH
Multi-ancestry Pangenome-based Genome Wide Association Study of Obstructive Sleep Apnea and Insomnia in the All of Us Research Program

Iganzio Piras (PI) 04/1/2027 – 03/31/2032
R01 $6,206,418
NIH
Peripheral drivers of Alzheimer's Disease revealed by patient serum exposure in human cerebral organoids

Kendall Van Keuren- Jensen (Co-I) 11/01/2027-10/31/2028
NA (Proitsi) $61,157
Alzheimer's Research UK via Queen Mary University of London, UK
Dissecting dementia co-pathologies: genetic and molecular determinants

Kendall Van Keuren- Jensen (PI) 04/01/2027 -03/31/2032
RM1 $12,950,072
NIH
Decoding Cellular Dysfunction in Human Biofluids

Kendall Van Keuren- Jensen (Co-I) 04/01/2027 – 03/31/2032
R01 (Medina) $614,991
NIH via St. Joseph's Hospital and Medical Center
Matrin 3 Loss-of-Function as a shared mechanism in neurodegenerative disease

Kendall Van Keuren- Jensen (Co-I) 12/01/2026-11/30/2028
R21 (Sattler) $129,999
NIH via St. Joseph's Hospital and Medical Center
TDP-43 Associated Synaptic RNA Splicing Defects in C9orf72FTD

Kendall Van Keuren- Jensen (Co-I) 07/01/2026 – 06/30/2031
P30AG072980 (Renewal Proposal) (Langbaum) $256,975
NIH via Banner Health
Arizona Alzheimer's Disease Research Center (ADRC)

Kendall Van Keuren- Jensen (PI) 07/01/2026-06/2027
NA $89,250
Arizona Department of Health Services via Banner Health
FY2027: Mapping proteinopathy-defined transcriptomes

Kendall Van Keuren- Jensen (Co-I) 07/01/2026-06/31/2036
HT9425FY25ALSRTTIA (Medina) $55,000
DoD via St. Joseph's Hospital and Medical Center
Targeting m6A dysregulation in ALS via small molecule approaches

Kendall Van Keuren- Jensen (Multi-PI) 07/01/2026 – 06/31/2031
R01 (Das) $1,920,000
NIH via Mass General Hospital
Tissue-specific Evs as liquid biopsy for systemic chronic diseases

Kendall Van Keuren- Jensen (Multi-PI) 04/01/2026 – 03/31/2031
RM1 (Gamazon) $2,880,000
NIH via Vandebilt University
The genomics of inter-organ and tissue communication via extracellular vesicles

Alexander, Gene E. (Co-I) 04/01/2026 - 03/31/2031
R01AG094088 (PI: Weinkauf) $7,469,211
NIA
Evaluation of Interaction and Time Course of Small and Large Vessel Cerebrovascular Contributions to Alzheimer's Disease Risk

Alexander, Gene E. (Co-I) 7/01/2026 - 06/30/2031
R01AG098268 (PI: MacLean) $3,876,958
NIA
IGF-1 as a Neuroprotective Factor for Cognitive Impairment in a Companion Dog Model of Alzheimer's Disease

Alexander, Gene E. (Core Co-Leader) 7/01/2026 - 06/30/2031
(PI: Langbaum) $799,845 TC UA Sub
NIA
Arizona Alzheimer's Disease Research Center-Biomarker Core

Barnes, Carol (PI) 05/01/2027-04/30/2032
NIH/NIA $1,712,490
Postdoctoral Training, Neurobiology of Aging and Alzheimer's Disease

Barnes, Carol (PI) 12/01/2026-11/30/2031
NIH/NIA $6,854,309
Neurobehavioral Relations in Senescent Hippocampus

Barnes, Carol (PI) 05/01/2026-04/30/2028
NIH/NIA $728,506
Frontal and Temporal Lobe Interactions in Rat Models of Normative Aging and Alzheimer's Disease

Bartlett, Mitchell J. PhD (Co-I) 05/01/2026-04/30/2029
Arizona Biomedical Research Centre (ABRC) $225,000 Total Project
New Investigator Award 26051579 (Bartlett)
ABRC via University of Arizona
Targeting the Cervical Lymphatics for the Treatment of Alzheimer's Disease: A Preclinical Pilot Study

Bartlett, Mitchell J. PhD (Co-I) 07/01/2026-06/30/2031
R01 (Hutchinson) $3,130,591
NIH via University of Arizona
Non-contrast slow flow MRI in the peripheral lymphatic system

Bartlett, Mitchell J. PhD (Co-I) 12/01/2026-11/30/2031
R01 (Polt) $2,897,567
NIH via University of Arizona
Truncated PACAP Glycosides as PAC1 Agonists with Therapeutic Potential

Bartlett, Mitchell J. PhD (Co-I) 07/01/2026-06/30/2027
Arizona Alzheimer's Consortium (AAC) (Polt) $30,000
AAC via University of Arizona
Evaluation of a 23-amino acid pituitary adenylate cyclase-activating peptide for the treatment of Alzheimer's disease

Bartlett, Mitchell J. PhD (Co-I) 07/01/2026-06/30/2027
Arizona Alzheimer's Consortium (AAC) (Porreca) $29,108
AAC via University of Arizona
Determining the impact of Alzheimer's disease and kappa-opioid receptor signaling on sleep fragmentation, sharp-wave ripple oscillations, and memory-trace reactivation

Bartlett, Mitchell J. PhD (PI) 07/01/2026-06/30/2027
The Bio5 Postdoctoral Fellowship (Bartlett) $5,000
University of Arizona Research Development Services via University of Arizona
Development of a Novel Surgical Treatment for Alzheimer's Disease

Barnes, Carol (PI) 05/01/2027-04/30/2032
NIH/NIA $1,712,490
Postdoctoral Training, Neurobiology of Aging and Alzheimer's Disease

Barnes, Carol (PI) 12/01/2026-11/30/2031
NIH/NIA $6,854,309
Neurobehavioral Relations in Senescent Hippocampus

Barnes, Carol (PI) 05/01/2026-04/30/2028
NIH/NIA $728,506
Frontal and Temporal Lobe Interactions in Rat Models of Normative Aging and Alzheimer's Disease

Bilgin, Ali (PI) 07/01/2026-06/30/2029
- (Bilgin) $750,000
Arizona Biomedical Research Centre
Noninvasive Longitudinal Assessment of MASH Under Pharmacologic Therapy Using Low-Field MRI

Chen, Nan-kuei (MPI) 07/01/2026-06/31/2031
NIH R01 AG104679 (Chen, Wen, Tong) $2,499,980
NIH/NIA
Sleep-Dependent Dynamics of CSF and Blood in Aging and Alzheimer's Brain

Chou, Ying-hui (PI) 01/01/2027-12/31/2031
P01 AG096875 (Chou) $3,792,268
NIH/NIA
Plasticity Reserve as a Predictor of Cognitive Decline in Relation to ATN Biomarkers in Preclinical and Prodromal Alzheimer's Disease

Hutchinson, Elizabeth (MPI) 07/01/2026-06/30/2031
1R01HL191072 (Hutchinson/Williamson) $2,169,868
NIH
Non-contrast slow flow MRI in the peripheral lymphatic system for Alzheimer's disease

Hutchinson, Elizabeth (Co-I) 07/01/2026-06/30/2031
5R01 AG073230 (Pires) $3,890,590
NIH
Mechanisms of cerebral vascular smooth muscle cell dysfunction in AD/ADRD

Hutchinson, Elizabeth (MPI) 04/01/2027-03/31/2029
1R21NS149668 (Hutchinson/Lifshitz) $384,292
NIH
Radiologic-pathologic correspondence of diffusion MRI markers for the rod microglial response following traumatic brain injury

Kielar, Aneta (PI) 09/01/2026-09/30/2030
FY26 AZRP Transforming Care Award $1,400,000
Funding Opportunity: HT942526AZRPTrCA
Defense Health Agency Research and Development (DHA R&D)-the Department of Defense, DOD
Congressionally Directed Medical Research Program (CDMRP)

Pires, Paulo W. (PI) 12/01/2026-11/30/2031
R01 HL191006 (Pires/Li) $3,848,165
NIH/NHLBI via The University of Arizona
ApoE4-Driven Vascular Smooth Muscle Cell Cholesterol Accumulation as a Central Mechanism in Cerebral Small Vessel Disease

Pires, Paulo W. (PI) 08/01/2026-05/31/2031
R01 AG098361 (Pires) $3,886,032
NIH/NIA via The University of Arizona
Mechanisms of cerebral vascular smooth muscle cell dysfunction in AD/ADRD

Pires, Paulo W. (MPI) 12/01/2026-11/30/2031
R01 AG107003 (Symons/Pires) $3,799,779
NIH/NIA via University of Utah
Targeting cerebral endothelial cell autophagy to limit age-related cerebrovascular dysfunction

Rodgers, Kathleen (Contact PI/ MPI) 12/01/2026–11/30/2031
1U01AG105523-01 $11,659,063
NIH/NIA
Translational Development of Lipoxin-Mimicking FPR2 Agonists for Alzheimer's Disease: From Lead Optimization through Phase I Clinical Trial

Rodgers, Kathleen (Project 3 Lead) 07/01/2026–06/30/2031
2P01AG026572-21 (Brinton) $3,736,780 Total Project
NIH/NIA
Perimenopause in Brain Aging and Alzheimer’s Disease | Project 3: Timing of Menopausal Hormone Therapy across Perimenopause to Menopause Transition: Impact on Neuroimmune System in Brain

Rodgers, Kathleen (Contact PI/ MPI) 04/01/2027–03/31/2032
Pending (Rodgers) $1,029,730 Total Project
NIH/NIA
ADRD Science Competence and Understanding for Teacher (SCOUT)

Savir-Baruch, Bital (PI) 04/01/2026 - 03/31/2031
R01 AG094088 $7,800,000 Total Project
Evaluation of Interaction and Time Course of Small and Large Vessel Cerebrovascular Contributions to Alzheimer's Disease Risk

Su, Judith (PI) 11/01/2026-10/31/2031
ARPA-H $9,039,600
Advanced Research Projects Agency for Health
Democratizing Human Microplastic and Nanoplastic Monitoring Through High-Throughput Multiscale Optical Sensing

Su, Judith (PI) 07/01/2027-06/30/2030
NSF TRAILBLAZER $3,000,000
National Science Foundation
Optical Sniffer Detection of Microbial-Driven Trace Gas Exchange to Understand Plant Ecosystems for Securing Climate-Stable Food and Water Systems

Su, Judith (PI) 04/01/2027-03/31/2031
NIH R35 $2,537,415
National Institutes of Health
Direct Measurement of Dynamic Molecular Interactions in Membrane Receptor Biology

Su, Judith (PI) 04/01/2027-03/31/2032
NIH RM1 $11,658,735
National Institutes of Health
Fundamental Mechanisms of Ectopic Chemosensory Receptor Signaling through Integrated Experimental and Computational Approaches

Su, Judith (PI) 04/01/2027-03/31/2031
NIH R01 $1,445,116
National Institutes of Health
Quantum Photonic Architectures for Frequency-Locked Whispering Gallery Mode Microtoroid Biosensing

Su, Judith (Co-I) 01/01/2027-12/31/2030
NIH R01 $856,997
National Institutes of Health
Quantum-Enhanced Ultra-Wide Field-of-View Microscopy for Measuring the Binding Kinetics of Low-Affinity Interactions

Su, Judith (PI) 04/01/2027-03/31/2029
NIH R21 $348,713
National Institutes of Health
Single-Particle Vibrational Spectroscopy Using Photothermal FLOWER Microscopy

Su, Judith (PI) 09/01/2025-09/30/2028
NSF CBET-EPSRC $450,000
National Science Foundation
Robust Free-space Driven Microtoroidal Arrays for Next Generation Biochemical Sensors (awarded, awaiting funds)

Su, Judith (MPI) 04/01/2027-03/31/2029
NIH $108,023
National Institutes of Health
AI-Guided Discovery of Multi-Target GPCR Ligands for the Treatment of Substance Use Disorders

Weinkauf, Craig (PI) 07/01/2026-03/31/2031
R01AG094088-01 $5,287,868
NIH/NIA via University of Arizona
Evaluation of Interaction and Time Course of Small and Large Vessel Cerebrovascular Contributions to Alzheimer's Disease Risk

Zhou, Wei (PI) 09/01/2026-08/31/2028
Pending $262,621Total Project
NIH/NIDDK via University of Michigan
Impact of cognitive function for DFU healing and recurrence

Christine Belden (Project Co-I) 07/01/2026-06/30/2027
Arizona DHS via Arizona Alzheimer’s Consortium $50,000
Returning Results to Research Participants

Claire Erickson (Project PI) 07/01/2026-06/30/2027
Arizona DHS via Arizona Alzheimer’s Consortium $55,556
Informing models for digital delivery of APOE and pTau-217 results: Data analysis of the eSMARTER study

Claire Erickson (Project Co-I) 07/01/2026-06/30/2027
Arizona DHS via Arizona Alzheimer’s Consortium $50,000
Returning Results to Research Participants

Jessica Langbaum (Project PI) 07/01/2026-06/30/2027
Arizona DHS via Arizona Alzheimer’s Consortium $50,000
Returning Results to Research Participants

Jessica Langbaum (Project PI) 07/01/2026-06/30/2027
Arizona DHS via Arizona Alzheimer’s Consortium $133,333
Alzheimer’s Prevention Registry and its GeneMatch Program

Jessica Langbaum (Project Co-I) 04/01/2027-03/31/2032
NIH via University of Pennsylvania (PI Greysen) $374,960

A Randomized Trial of Gamification to Increase Mobility in Seniors with High Risk for Alzheimer's Disease

Jessica Langbaum (Project Co-I) 04/01/2027-03/31/2032
NIH via University of Pittsburgh (PI Cohen) $1,127,641
Alzheimer's Biomarker Consortium—Autism (ABC-A)

Jessica Langbaum (Project Co-I) 04/01/2027-03/31/2032
NIH (PI Tariot) $30,750,654
Immunomodulatory Therapy with BCG to Prevent Progression of Preclinical Alzheimer's Disease

Jessica Langbaum (Project PI) 07/01/2026-06/30/2031
NIH/NIA P30AG072980 Renewal (PI Langbaum) $22,777,142
Arizona Alzheimer's Disease Research Center

Jessica Langbaum (Co-I) 07/01/2026-06/30/2031
NIH via University of Washington $175,000
(MPIs Stephens, Crane, Shojaie)
National Alzheimer's Coordinating Center (NACC)

Jessica Langbaum (Co-I) 07/01/2026-06/30/2031
NIH via Washington University Saint Louis $125,000
(MPIs Biber, Kukull et al)
National Alzheimer's Coordinating Center (NACC)

Michael Malek-Ahmadi (Co-I) 07/01/2026-06/30/2027
State of Arizona DHS via Arizona Alzheimer's Consortium $44,444
Mentorship of Arizona Undergraduate and Graduate Students in ADRD Research

Michael Malek-Ahmadi (Co-I) 07/01/2026-06/30/2027
State of Arizona DHS via Arizona Alzheimer's Consortium $22,222
Impact of Early Exposure to Cholinesterase-Inhibitors on Clinical Trajectories, Milestones and Mortality in Autopsy-Supported Alzheimer's Disease

Michael Malek-Ahmadi (Co-I) 07/01/2026-06/30/2027
State of Arizona DHS via Arizona Alzheimer's Consortium $244,444
Clinical and Biological Characterization of The Longevity Cohort Study: Global Staging and Biospecimen Banking

Michael Malek-Ahmadi (Co-I) 07/01/2026-06/30/2027
State of Arizona DHS via Arizona Alzheimer's Consortium $100,000
Statistical and Image Analysis Resource for Alzheimer's Researchers Inside and Outside of Arizona

Michael Malek-Ahmadi (Co-PI) 04/01/2027-03/31/2032
NIH/NIA $1,082,000
Building the Next Generation Dementia-Focused Workforce through the Banner-ASU Neuroscience Scholars Program

Michael Malek-Ahmadi (Co-I) 07/01/2026-06/30/2031
NIH/NIA via Arizona State University $106,690
Objective Assessment of Daily Function in Alzheimer's Disease: A Novel, Remote, Performance-Based Approach

Michael Malek-Ahmadi (Co-I) 07/01/2026-06/30/2031
NIH/NIA via Arizona State University $261,799
Advanced Early Detection of Alzheimer's Disease Through Integrative Computational dMRI Analysis of Motor Deficits Across Rodent and Human Models

Michael Malek-Ahmadi (Co-I) 07/01/2026-06/30/2031
NIH/NIA P30AG072980 Renewal (Langbaum) $22,777,142
Arizona Alzheimer's Disease Research Center – Data Management and Statistics Core

Michael Malek-Ahmadi (Co-I) 07/01/2026-06/30/2028
NIH/NIA via AARC $36,830
Spatial Transcriptomics to Assess Gene Expression Changes by Disease State

Michael Malek-Ahmadi (Co-I) 04/01/2027-03/31/2032
NIH via Arizona State University $321,369
Neuroimaging and plasma correlates of motor-based assessments for early dementia risk screening

Jeremy Pruzin 07/01/2026-06/30/2027
State of Arizona DHS via Arizona Alzheimer's Consortium $33,333
Dementia Untangled Podcast as a Psychoeducational Intervention: Secondary Analyses, Dissemination, and Preparation for an NIH-Funded Efficacy Trial

Eric Reiman (Co-I) 12/01/2026-11/30/2031
NIH/NIA (Su) $4,998,512
Individualized Predictive Modeling of Brain Aging and Alzheimer's Disease Trajectories

Eric Reiman (Co-I) 07/01/2026-06/30/2031
NIH/NIA P30AG072980 Renewal (PI Langbaum) $22,777,142
Arizona Alzheimer's Disease Research Center

Yi Su (Site PI) 05/01/2026-04/30/2031
NSF via Arizona State University $974,375
Integrating Structural MRI and Blood-Based Biomarkers for Alzheimer's Disease: Resolving Amyloid Uncertainty and Predicting Longitudinal Progression

Yi Su (Co-I) 06/01/2026-05/31/2029
Arizona DHS via BNI Dignity $44,529
Multiparametric MRI for Prediction of Adjacent Segment Degeneration

Yi Su (Co-PI) 07/01/2026-06/31/2027
Arizona DHS via Arizona Alzheimer's Consortium $100,000
Statistical and Image Analysis Resource for Alzheimer's Researcher's Inside and Outside of Arizona

Yi Su (Co-PI) 07/01/2026-06/30/2027
Arizona DHS via Arizona Alzheimer's Consortium $55,556
Predicting Risk of Cognitive Impairment Leveraging Blood-Based Biomarkers

Yi Su (Co-I) 07/01/2026-06/30/2027
Arizona DHS via Arizona Alzheimer's Consortium $302,889
Advanced Imaging Data Analysis and ML/AI in Alzheimer's Research

Yi Su (Co-PI) 07/01/2026-06/30/2027
Arizona DHS via Arizona Alzheimer's Consortium $45,000
Automating Centralized Data Management Program for Arizona's Alzheimer's Disease and Related Studies

Yi Su (Co-PI) 07/01/2026-06/30/2027
Arizona DHS via Arizona Alzheimer's Consortium $44,444
Mentorship of Arizona Undergraduate and Graduate Students in ADRD Research

Yi Su (Co-I) 07/01/2026-06/3/2031
NIH/NIA via University of Missouri $1,201,532
Neurodegeneration in Adult autism: a multi-modal biomarker investigation of Alzheimer's and Parkinson diseases

Yi Su (Co-PI) 07/01/2026-06/30/2031
NIH/NIA P30AG072980 Renewal (Langbaum) $22,777,142
Arizona Alzheimer's Disease Research Center - DMSC, Biomarker Core

Yi Su (PI) 12/01/2026-11/30/2031
NIH/NIA $4,998,512
Individualized Predictive Modeling of Brain Aging and Alzheimer's Disease Trajectories

Yi Su (Site PI) 04/01/2027-03/31/2032
NIH via MGH (Quiroz) $215,780
The Boston Latino Aging Study (BLAST): Understanding Alzheimer's risk and biomarkers in older Latinos

Yi Su (PI) 04/01/2027-03/31/2032
NIH/NIA $767,166
AI-AD Bidirectional Data Leadership Academy

Yi Su (Site PI) 04/01/2027-03/31/2032
NIH via TGEN $3,477,837
Rural-Urban Differences in Cognitive Aging: Multimodal Predictors of Decline and Resilience

Nicholas Ashton (Co-I) 01/01/2027-12/31/2028
The Association for Frontotemporal Degeneration via UCSF (Saloner) $267,797
Targeted Immunoassay Validation of CSF MMP10, ISG15, and HOMER1 for FTLD-TDP and FTLD-tau Subtype Diagnosis

Nicholas Ashton (Co-I) 12/1/2026-11/30/2031
NIH via University of Arizona (Chou) $389,160

Plasticity Reserve as a Predictor of Cognitive Decline in Relation to ATN Biomarkers in Preclinical and Prodromal Alzheimer's Disease

Nicholas Ashton (Co-I) 12/01/2026-11/30/2031
NIH via Boston University (Au) $337,401
Precision Brain Health Monitoring for Alzheimer's Disease Risk Detection & Prevention

Nicholas Ashton (Co-I) 12/01/2026-11/30/2031
NIH via University of Wisconsin-Madison (Zetterberg) $251,883
TDP-43 Biomarkers for Neurodegenerative Diseases: Discovery and Validation

Nicholas Ashton (Co-I) 10/01/2026-09/2027
NIH via University of Arizona (Chou) $33,255
Plasticity Reserve in Alzheimer's Disease: Longitudinal Insights from Preclinical and Prodromal Stages

Nicholas Ashton (Co-I) 07/01/2026-06/30/2031
NIH via University of Pennsylvania (Serper) $252,215
Investigations of Alzheimer's Disease in Liver Disease and Transplantation: The LivCog Biomarker Study

Nicholas Ashton (Co-I) 07/01/2026-06/30/2031
NIH via Utah University (Pruzin) $1,253,987
Neuroprotective Mechanisms of ARBs and ACEIs: Examining Blood Biomarkers of Vascular Contributions to Cognitive Impairment, Alzheimer's Disease, and Neurodegeneration

Nicholas Ashton (Co-I) 07/01/2026-06/30/2031
NIH/University of Missouri (Beversdorf) $1,201,532
Neurodegeneration in adult autism: a multi-modal biomarker investigation of Alzheimer and Parkinson diseases

Nicholas Ashton (Co-I) 07/01/2026-06/30/2031
NIH/NIA P30AG072980 Renewal (Langbaum) $22,777,142
Arizona Alzheimer's Disease Research Center

Nicholas Ashton (Co-I) 05/01/2026-04/30/2028
The Association for Frontotemporal Degeneration $300,395
via UMiami Jacksonville (Petrucelli)
TDP-43 Cryptic Targets in FTD

Nicholas Ashton (Co-I) 07/01/2026-06/30/2027
C-Path Institute via Arizona Alzheimer's Consortium $19,060
Longitudinal and predictive modeling of CSF proteomics in PSEN1 E280A mutation carriers

Nicholas Ashton (PI) 07/01/2026-06/30/2027
AZ DHS via Arizona Consortium (AAC) $130,000
A Resource of Alzheimer's Disease Fluid Biomarker Expertise and Assays for Researchers in the Arizona Alzheimer's Consortium

Nicholas Ashton (PI) 07/01/2026-06/30/2027
AZ DHS via Arizona Consortium (AAC) $55,556

DROP-AD: A capillary blood test for Alzheimer's disease pathology

Nicholas Ashton (Co-I) 07/01/2026-06/30/2031
NIH via Boston University (Au) $3,388,968
Prognostic Model to Distinguish AD from AD+LATE Using Plasma AD Biomarker, Imaging, and Cognition

Nicholas Ashton (Co-I) 05/01/2026-04/30/2031
NSF (Su) $974,375
Integrating Structural MRI and Blood-Based Biomarkers for Alzheimer's Disease: Resolving Amyloid Uncertainty and Predicting Longitudinal Progression

Nicholas Ashton (Co-I) 04/01/2026-03/31/2031
NIH via Arizona State University (Wang) $456,015
Deep Learning-Based Retinal Imaging Screening Tool for Preclinical Alzheimer's Disease

Alireza Atri (Project Co-I) 07/01/2026-06/30/2027
Arizona Alzheimer's Consortium $55,556
via Arizona DHS (Choudhury)
Clinical trajectories and associations with pathology in Lewy body spectrum disorders

Alireza Atri (Project PI) 07/01/2026-06/30/2027
Arizona Alzheimer's Consortium via Arizona DHS $244,444
Clinical Phenotyping and Biological Characterization of The Longevity Cohort Study: Global Staging and Biospecimen Banking

Alireza Atri (Project PI) 07/01/2026-06/30/2027
Arizona Alzheimer's Consortium via Arizona DHS $77,778
Development, Validation and Implementation of Cognitive and Clinical Composites for the Arizona Study of Aging and Neurodegenerative Disorders/BBDP

Alireza Atri (Project Co-I, Core Leader) 07/01/2026-06/30/2031
NIH/NIA P30AG072980 Renewal (Langbaum) $22,777,142
Arizona Alzheimer's Disease Research Center

Alireza Atri (Project Co-I) 04/01/2027-03/31/2032
NIH/NIA via Fordham University (Rivera Mindt) $949,186
Biomarker Evaluation in Young Onset NeuroDegeneration for Early Detection (BEYONDD)

Alireza Atri (Project Co-I) 04/01/2027-03/31/2032
NIH/NIA via Johns Hopkins University (Hanley) $535,033
MANS: MW150 Neurocognitive Studies

Alireza Atri (Project Co-I) 04/01/2027-03/31/2032
NIH via TGEN (Huentelman) $3,477,837
Rural-Urban Differences in Cognitive Aging: Multimodal Predictors of Decline and Resilience

Alireza Atri (Project Co-I) 12/01/2026-11/30/2031
NIH via Washington University St. Louis (Bateman) $353,315
DIAN-TU Amyloid Removal Trial (ART) in Dominantly Inherited Alzheimer's Disease

Alireza Atri (Project Co-I) 07/01/2026-06/30/2031
NIH/NIA via Johns Hopkins University (Hanley) $430,442
STORM: Proof-of-concept STudies of ORal MW189, a novel anti-neuroinflammatory drug, in Alzheimer's Patients

Alireza Atri (Project Co-I) 07/01/2028-06/30/2031
NIH/NIA via Brigham and Women's Hospital (Basin) $270,000
Repurposing a Combination Antiretroviral Drug Therapy to Target Retrotransposons and Treat Early Alzheimer's Disease: A Two-Phase UG3/UH3 Clinical Drug Development Program

Alireza Atri (Project Co-I) 01/01/2027-12/31/2027
NIH/NIA via University of Delaware(Tulsky) $77,950
Development of Measure(s) of Financial Hardship and Health Disparities among Individuals Living with ADRD and Their Family Caregivers

Thomas Beach (Site PI) 07/01/2026-06/31/2028
NIH via UGA (Kanthasamy) $93,050
Role of Nuclear Pore Complex Dysfunction in Neurotoxic Pesticide induced Pathogenesis of ADRD

Thomas Beach (Site PI) 12/01/2026-11/30/2031
NIH via Stanford University (Soto) $180,077
Alpha-synuclein seed amplification assay as a biomarker for Lewy body dementia and Alzheimer's disease

Thomas Beach (Site PI) 12/01/2026-11/30/2031
NIH via UCLA (Videlock) $32,236
Defining the Role of Endogenous Enteric proSAAS in Parkinson's Disease

Thomas Beach (Site PI) 01/01/2027-12/31/2028
NIH via NJIT (Chen) $31,286
Quantitative Assessment of Nanoplastics in Alzheimer's Disease Brain and Their Role in Amyloid-β Aggregation

Thomas Beach (Site PI) 04/01/2027-03/31/2032
NIH 5R01AI162850 Renewal via BU (Mizgerd) $201,046
Pulmonary pathophysiology sub-phenotypes of pneumonia

Thomas Beach (Core Leader) 07/01/2026-06/30/2031
NIH/NIA P30AG072980 Renewal (Langbaum) $22,777,142
Arizona Alzheimer's Disease Research Center-Biomarker Core

Thomas Beach (Co-I) 04/01/2027-03/31/2032
NIH via Rush University (Romanova) $255,791
Clearance of Alzheimer's disease biomarkers by arachnoid cells

Thomas Beach (Site PI) 09/01/2026-08/30/2028
MJFF-029023 $217,784
Assessment of Persistent Industrial Organic Chemicals in Postmortem Organs from PD & Control Subjects

Thomas Beach (Site PI) 12/01/2026-11/30/2031
NIH via UTHealth (Pritzkow) $181,137
Using the seed amplification assay to detect dementia with Lewy bodies and differentiate from other Alzheimer's related dementias

Thomas Beach (Co-I) 03/01/2026-02/28/2031
NIH/NIA via University of Wisconsin-Madison $392,870
R01AG070883 Renewal (Kind)
The Neighborhoods Study: Contextual Disadvantage and Alzheimer’s Disease and Related Dementias

Thomas Beach (Site PI) 07/01/2026-06/31/2028
NIH via UGA (Kanthasamy) $93,050
Multi-omics Profiling of the Pancreatic Neuroendocrine Axis in Parkinson's Disease

Thomas Beach (Site PI) 12/01/2025-11/31/2027
NIH via MSSM (Bendl) $54,000
Natural lineage recording via somatic mosaicism to decipher macrophage entry in aging and AD

Parichita Choudhury (Project Co-I, Core Leader) 07/01/2026-06/30/2031
NIH/NIA P30AG072980 Renewal (Langbaum) $22,777,142
Arizona Alzheimer's Disease Research Center

Parichita Choudhury (Co-PI) 04/01/2027-03/31/2032
NIH/NIA $1,082,000
Building the Next Generation Dementia-Focused Workforce through the Banner-ASU Neuroscience Scholars Program

Parichita Choudhury (Project PI) 07/01/2026-06/30/2027
Arizona Alzheimer’s Consortium via Arizona DHS $55,556
Clinical trajectories and associations with pathology in Lewy body spectrum disorders

Parichita Choudhury (Project Co-I) 07/01/2026-06/30/2027
Arizona Alzheimer’s Consortium via Arizona DHS (Atri) $244,444
Clinical Phenotyping and Biological Characterization of The Longevity Cohort Study: Global Staging and Biospecimen Banking

Parichita Choudhury (Project Co-I) 07/01/2026-06/30/2027
Arizona DHS via Arizona Alzheimer’s Consortium (Ho) $22,222
Impact of Cholinesterase-Inhibitors on Clinical Trajectories, Milestones and Mortality in Autopsy-Supported Alzheimer’s disease

Andrew Ho (Project PI) 07/01/2026-06/30/2027
Arizona DHS via Arizona Alzheimer’s Consortium $22,222
Impact of Cholinesterase-Inhibitors on Clinical Trajectories, Milestones and Mortality in Autopsy-Supported Alzheimer’s disease

Geidy Serrano (Project PI) 07/01/2026-06/30/2027
Arizona DHS via Arizona Alzheimer’s Consortium $258,445
Patient-based live cell banking for translational research

Geidy Serrano (Site PI) 04/01/2027-03/31/2032
NIH via McLaughlin Research (Leavens) $54,584
Aberrant Superoxide Dismutase 1 and Cysteine Oxidation in Parkinson's Disease

Geidy Serrano (Site PI) 04/01/2027-03/31/2032
NIH via Rush University (Romanova) $255,791
Clearance of Alzheimer’s disease biomarkers by arachnoid cells

Geidy Serrano (Site PI) 04/01/2027-03/31/2032
NIH via Michigan State University (Benskey) $153,412
Investigating the Therapeutic Potential of Complement Inhibition in the Context of Synucleinopathy

Geidy Serrano (Site PI) 04/01/2027-03/31/2032
NIH via Arizona State University (Mastroeni) $278,163
Multi-Organ Burden and Biological Effects of Micro and Nanoplastics in Human Aging and Alzheimer’s Disease

Geidy Serrano (Site-PI) 04/01/2027-03/31/2032
NIH/University of Arizona $40,875
R01AG072643 Renewal (Barnes)
NPTX2: Preserving memory circuits in normative aging and Alzheimer's Disease

Geidy Serrano (Site-PI) 04/01/2027-03/31/2032
NIH via TGEN (Piras) $1,626,511
Peripheral drivers of Alzheimer’s Disease revealed by patient serum exposure in human cerebral orgnoids

Geidy Serrano (Site-PI) 04/01/2027-03/31/2032
NIH via UTHealth (Shanawaz) $245,605
Size Distribution and Characterization of Pathogenic α-Synuclein Aggregates in Human CSF

Geidy Serrano (Site-PI) 04/01/2027-03/31/2032
NIH via Stonybrook (Restrepo) $245,605
Cerebellar Mechanisms Underlying Motor Decline in Mild Cognitive Impairment

Geidy Serrano (Co-PI) 09/01/2026-08/30/2028
MJFF-029023 $217,784
Assessment of Persistent Industrial Organic Chemicals in Postmortem Organs from PD & Control Subjects

Geidy Serrano (Site PI) 03/01/2026-02/28/2031
NIH/NIA via University of Wisconsin-Madison $392,870
R01AG070883Renewal (Kind)
The Neighborhoods Study: Contextual Disadvantage and Alzheimer’s Disease and Related Dementias

Geidy Serrano (Core Leader) 07/01/2026-06/30/2031
NIH/NIA P30AG072980 Renewal (Langbaum) $22,777,142
Arizona Alzheimer’s Disease Research Center-Biomarker Core

Geidy Serrano (Site PI) 04/01/2026-03/31/2031
NIH via University of Birmingham Alabama (Rizzardi) $72,306
Investigating the role of ZEB1 in Alzheimer's disease

Geidy Serrano (Site PI) 04/01/2026-03/31/2031
NIH via UCLA (Rexach) $105,648
Ultra High-Resolution Multimodal Cross-Disorder Atlas of Neurodegenerative Dementias

Madeline Andrews, PI 7/1/2026-6/30/2028
FP00049496 $394,595.00
HHS: National Institutes of Health (NIH)
Leveraging aged organoids to study metabolic drivers in degeneration onset Total Project

Madeline Andrews, PI 8/1/2026-7/31/2028
FP00049651 $3,677,116.00
HHS: National Institutes of Health (NIH)
Glucose & oxygen metabolism regulate human cortical progenitor development impacting brain health

Madeline Andrews, PI 12/1/2026-11/30/2031
FP00050652 $3,230,236.00
HHS: National Institutes of Health (NIH)
Metabolic signal integration regulates stem cell quiescence and fate in human cortical

Madeline Andrews (Co-I), Mehdi Nikkhah (PI) 12/1/2026-11/30/2031
FP00051778 $3,413,708.00
Understanding the Aging Vascular Contribution to AD through Medin Signaling using On-Chip Microphysiological Systems

Madeline Andrews, PI 11/1/2026-10/31/2027
FP00052129 $25,000.00
Brain Aneurysm Foundation
Deconstructing Brain Injury from Aneurysmal Subarachnoid Hemorrhage with Organoids

Madeline Andrews, PI 4/1/2027-3/31/2032
FP00052395 $3,627,302.00
Award Sponsor: HHS: National Institutes of Health (NIH)
Project/Grant Title: Metabolic regulation of human cortical progenitor development

PI: Rangasamy (ASU/TGEN) Funded/Pending Start Date
Co-Investigator: Heather Bimonte-Nelson
NIH R21NS145159
Mitochondrial Methionyl-tRNA Formyltransferase (MTFMT) Mouse Model to Elucidate Mitochondrial Translation Initiation Defect and Disease Mechanisms in Leigh Syndrome

PI: Brafman 07/01/2026-06/30/2028
NIA- 1R21AG101719-01 $431,750
Defining the Mechanisms Underlying the Protective Effects of the Reelin-COLBOS Variant in Alzheimer's Disease (AD)

PI: Brafman 12/01/2026-11/30/2031
NIA-1R01AG106273 $3,926,958
Stabilized Programmable RNA Sensors for Primer-Free SNP Detection at the Point of Care

PI: Brafman 12/01/2026-11/30/2028
NIA- 1R21AG100556-01A1 $431,750
Dissecting Cell-Type-Specific Roles of RAB10 in Endo-Lysosomal Trafficking and Alzheimer's Disease Pathogenesis

PI: Brafman 12/01/2026-11/30/2028
NIA- 1R21AG108206-01 $431,750
Human iPSC Models to Define MAPT Haplotype Effects in Alzheimer's Disease

Sadleir (Contact PI), Zhou (MPI), Beeman (MPI) 05/01/27-04/30/32
1R01AG096642-01 $2,500,000
Conductivity Tensor Imaging as an early biomarker for Alzheimer’s Disease

Jui-Heng Tseng (PI) 12/01/2026-11/30/2028
1R21AG105699-01 NIH/NIA $431,055
Acetylated tau as a driver of mitochondrial dysfunction in neurodegeneration

Jui-Heng Tseng (PI) 04/01/2027-03/31/2032
R01 NIH/NIA $3,297,703
Tau modification and neuronal vulnerability in brain aging and Alzheimer’s disease

Jui-Heng Tseng (PI) 07/01/2026- 06/30/2029
New Investigator Award $225,000
Arizona Biomedical Research Center
Targeting tau progression in age-related neurodegeneration

Jessica Verpeut, PI 6/1/2026 – 05/31/2029
FP49594 (Verpeut) $224,997
Arizona Biomedical Research Centre
Cerebellar proteoglycan dysfunction during the progression of Alzheimer’s disease

Jessica Verpeut, PI 7/1/2026 – 06/30/2027
FP52320 (Verpeut, Subcontract PI, Perez, PI) $52,994
Dignity Health-St. Joseph’s Hospital-BNI: Barrow Neurological
Foundation (BNF) / Arizona Alzheimer’s Consortium (AAC)
Cerebellar Perineuronal Net Dysfunction in Prodromal Alzheimer's Disease

Jessica Verpeut, PI 7/1/2026 – 06/30/2027
FP51565 (Coon) $72,000
Arizona Alzheimer's Consortium (AAC) / Arizona Department of Health Services (ADHS)
Spatial transcriptomic analysis of the cerebellum in Alzheimer’s Disease

Jessica Verpeut, PI 7/1/2026 – 06/30/2028
FP50223 $188,400
Arizona Alzheimer’s Disease Research Center (ADRC)
AAC Behavioral and blood biomarkers in a preclinical rodent model of Alzheimer’s disease

Jessica Verpeut, Co-I; Schaefer, PI — 4/1/2027-03/31/2032
FP52654 — $3,740,491
National Institutes of Health
Characterizing the timing and microstructural basis of motor deficits in Alzheimer's disease using diffusion magnetic resonance imaging

Wang/Dumitrascu (MPI) — 4/01/2026-3/30/2031
HHS: National Institutes of Health (NIH) — $3,807,810.00
Deep Learning-Based Retinal Imaging Screening Tool for Preclinical Alzheimer's Disease

Wang/Su (PI) — 7/1/2026-6/30/2031
HHS: National Institutes of Health (NIH) — $1,897,905.00
CRCNS: Integrating MRI and Blood Biomarkers for Amyloid Ambiguity and Progression