ARIZONA ALZHEIMER'S CONSORTIUM

# Annual Report

## July 1, 2023 - June 30, 2024

## and

# 25th Annual Scientific Conference

## September 12, 2024

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# Introduction to the Annual Report

## A Special Year

In several respects, this is a special year for the state and organizationally supported Arizona Alzheimer's Consortium (AAC) and its National Institute on Aging (NIA)-sponsored Arizona Alzheimer's Disease Research Center (ADRC).

As we prepare to hold our 25th Annual Scientific Conference, we are reminded of the continued progress, productivity, growth of the Consortium, ADRC and 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 disease (AD) and related diseases (ADRD). This year's conference will include more than 500 participants and more than 150 scientific abstracts and presentations. We are honored to have Michael Weiner, founding director of the AD Neuroimaging Initiative (ADNI) and a pioneer in the field, give this year's Leon Thal Memorial Lecture. This Lecture is named for one of the Consortium's original advisors, Leon Thal, who in addition to his other seminal contributions to the fight against AD, was Michaels's close friend and partner in the establishment of ADNI, and who played major roles in our state-wide Consortium's success.

An important indicator of an organization's maturation and success is its ability to develop and recruit new leaders to support its longstanding goals, find ways to refresh and enhance it, and aim to address even more breathtaking goals. One can see that indicator of success in its developing and newly recruited leaders. As reflected in this year's Scientific Conference and Annual Report, our Consortium and ADRC have benefitted from a growing number of established and emerging leaders.

We are delighted to announce that, in accordance with a longstanding succession plan, Jessica Langbaum became Director of the NIA-sponsored Arizona ADRC on July 1, 2024. Jessica is an internationally recognized leader in Alzheimer's prevention research, the science of research participant engagement research, and the disclosure of a person's genetic and biomarker risk for AD. She is also valued by collaborators inside Arizona and around the world for her approach to research collaboration. Jessica will be supported by Eric Reiman (the ADRC's original director), Alireza Atri, and a remarkable team of established and emerging ADRC leaders, as they work together to prepare for the submission of the ADRC's next five-year $30M competitive National Institute on Aging (NIA) renewal grant application in September 2025.

In the meantime, Eric will continue to serve as Director of the state- and organizationally supported AAC, support Jessica and their ADRC colleagues, and focus on the effort to find effective prevention therapies in the next few years, help fulfill the promise of blood biomarkers in the scientific and clinical fight against AD and ADRD, and provide a foundation for the organizations' longstanding productivity and impact in AD/ADRD research.

Based on some extraordinary developments in the last few years, the Consortium has placed a growing emphasis on the role of emerging blood-based biomarkers (BBBMs) in the scientific and clinical fight against AD, complementing its leadership roles in other areas. We are excited to announce that Nicholas Ashton recently moved from the University of Gothenburg in Sweden to establish what will quickly become one of the world's premier academic programs for the

discovery and high-throughput, high-quality assessment of blood (and cerebrospinal fluid [CSF]) biomarkers in the fight against AD and ADRD. Nicholas is internationally recognized for his productivity, impact and leadership role in this rapidly developing field, embraces our Consortium's collaborative values, and has already begun to work closely with our colleagues inside and outside the state to have a transformational impact on the field.

In addition to the advancement of blood-based biomarkers, this has been a remarkable time for the advancement of AD-modifying and prevention therapies. Based on these developments, Arizona researchers recently noted that there is a realistic chance to a) find and support the approval, coverage, and widespread accessibility of the first "secondary AD prevention therapies" (i.e., amyloid plaque-reducing antibody drugs that are given to cognitively unimpaired persons with blood test evidence to avert the onset of cognitive impairment) in 2-3 years); b) find and support the approval and widespread accessibility of the first "primary AD prevention therapy" (i.e., a subcutaneous amyloid plaque-reducing antibody therapy administered as infrequently as once per year to avert the onset of amyloid plaques and ensuing biological and clinical manifestations of AD almost completely within 5 years); and c) address the scientific, regulatory, payor, and policy challenges that need to be addressed to meet those goals (Reiman et al, *Lancet Neurol* 2024). Arizona researchers continue to play leadership roles in each of these collaborative endeavors. Complementing these efforts, they recently received a $75M NIA grant award for their next prevention trial in the world's largest autosomal dominant AD (ADAD) kindred in Colombia.

At this important time in the history of our Consortium and ADRC, we want to take a moment to acknowledge our longstanding external advisors, Marilyn Albert, Zaven Khachaturian, Bruce Miller and Thomas Montine, as well as our former advisors Leon Thal, Allen Roses, and Richard Frackowiak, who had an extraordinary impact on our collaborative model, scientific productivity, and impact. We could not be more grateful to them for their many years of service (far longer than any of them probably expected), extraordinary kindness, generosity and contributions. They have set an incredibly high standard for our future advisors.

**Background**

The AAC is the nation's leading model of statewide collaboration in AD research. It includes more than 250 researchers, clinicians, and staff from 14 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 six formally affiliated organizations include Banner Alzheimer's Institute-Tucson (BAI-T), the Critical Path Institute (CPATH), Midwestern University, Northern Arizona University (NAU), TGen North, 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 intended to make a transformational difference in the scientific fight against AD and ADRD, engage Arizona's Hispanic/Latino, American Indian, and other understudied and underserved communities, help address the unmet needs of patients and family caregivers, and advance the understanding and promotion of healthy cognitive aging. The Consortium's major themes include the unusually early detection, study, and prevention of AD, the study of brain aging, and the emerging roles of BBBMs in these and related endeavors. Its primary goal is to find effective AD prevention therapies within the next few years.

The Consortium is widely recognized as a model of multi-institutional collaboration in biomedical research. It is also recognized for the vision, groundbreaking contributions, productivity, impact, and leadership roles in its areas of emphasis. 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 NIA-

sponsored Arizona ADRC, and numerous other grants, contracts, and organizational and philanthropic investments.

As previously noted, Eric Reiman is the longstanding Director of the Consortium. Jessica Langbaum is the new Director of the ADRC. Carol Barnes chairs the Consortium's 24-member Internal Scientific Advisory Committee (ISAC). David Jerman is the Administrative Director of the Consortium's state and organizationally supported research Consortium; Winnie Liang assumed the role of Administrative Director of the NIA-sponsored Arizona ADRC in July 2024 and working closely with David, continues to have an administrative leadership role for the Consortium. Andrea Schmitt is the Grants Director for the NIA-sponsored Arizona ADRC. Leading officials from each of the Consortium's principal organizations serve on its Board of Directors. As previously noted, the Consortium and ADRC has continued to benefit greatly from our longstanding external advisors, internationally recognized for their contributions to and leadership roles in the study of AD and ADRD, who 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.

The AAC capitalizes on the state's strengths in brain imaging, emerging blood-based and other biomarkers, genomics, computational, mathematical, statistical, artificial intelligence/machine learning, 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 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. The Arizona ADRC's Administrative, Clinical, Data Management and Statistics, Biomarker, Neuropathology, and Outreach, Recruitment and Engagement Cores provides 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 and ADRD. While the early detection and prevention of AD and age-related cognitive decline continue to be our over-arching themes, the ADRC has placed additional emphases on the development, validation, and use of BBBMs in the early detection, tracking,

diagnosis, study, treatment and prevention of AD/ADRD, and their generalizability to under-represented groups.

The Arizona ADRC has six specific aims: 1) To optimize our ADRC cores, extensively share our data and samples, forge innovative and impactful multi-institutional, multi-disciplinary collaborations, to capitalize on and support our growing statewide collaborative research program, and make a profound difference in the fight against AD/ADRD. 2) To capitalize on major state, organizational and philanthropic commitments to augment and leverage our cores, further address our ADRC goals, and enhance our ability to address these goals. 3) To attract, train and support the next generation of ADRD researchers and clinicians, including those from diverse backgrounds. 4) To provide extensive outreach and education programs for healthy adults, patients, and family caregivers, including those from Arizona's Hispanic/Latino and American Indian communities, actively support their participation in AD/ADRD/brain aging research, and advance the use of BBBMs in these understudied groups. 5) To provide leadership and support for NIA-supported programs, other ADRCs, and the National Plan to Address AD. 6) To help set the stage for BBBMs to transform AD/ADRD research, treatment development and clinical care, inform the study of preclinical AD, and help provide the best possible chance to find and support the accelerated approval of an AD prevention therapy in the next five years.

Together, our Arizona ADRC grant, an NIA grant for the study of cognitively unimpaired persons at six levels of genetic risk based on their APOE genotype, a Gates Ventures grant, other major NIH grants, and state, organizational and philanthropic funds permit our researchers to provide shared resources of data and biological samples for neuropathological study and diagnostic validation of BBBMs for AD/ADRD, including blood samples from several hundred brain donors in the last years of life who have comprehensive neuropathological assessments after they die. In addition to their other contributions, ADRC and Consortium funds provide data and biological samples needed to confirm the accuracy of BBBMs in Hispanic/Latino and American Indian participants using cerebrospinal fluid (CSF) and brain imaging measurements, setting the stage to dramatically increase the use of biomarkers in these and other underrepresented groups. 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 BBBMs in independently funded studies. Some (but not all) of our developing resources are summarized in the table below:

| | Clinical Core (550 participants) | Affiliated BBDP (500 participants) | Affiliated APOE Program (300 participants) | APOE4/APOE2 Allelic Dose Cohort (300 participants) | Total (1,650 participants) |
|---|---|---|---|---|---|
| UDS Assessments | All, Annual NACC-Shared | All, Annual NACC-Shared | All, Biennial NACC-Shared | All, Biennial[1] NACC-Shared | All, Longitudinal NACC-Shared |
| Participants with Aβ and Tau PET | 100 NACC-Shared | 100 NACC-Shared | - | All, Biennial NACC-Shared | 500 NACC-Shared |
| Participants with MRIs | All NACC-Shared | 100 NACC-Shared | - | All, Biennial NACC-Shared | 950 NACC-Shared |
| Participants with CSF Samples | 275 NCRAD-Shared | 200 NCRAD-Shared | - | All, Biennial NCRAD-Shared | 775 NCRAD-Shared |
| Participants with Blood Samples | Nearly All, Annual NCRAD-Shared | Nearly All, Annual BSHRI-Shared | Near All, Annual Mayo-Shared | Nearly All, Annual NCRAD-Shared | Nearly All, Annual NCRAD-Shared |
| BBDP Enrollees[2] | ~300 | ~500 | TBD | TBD | ≥800 |
| Primary Funding Sources | ADRC & Gates | Organizations, State, Gates & Cost Recovery Fees | Organizations & State | Pending NIA Grant | - |

1 Participants who progress to MCI or dementia will be invited to enroll in Clinical core and have annual assessments
2 ~13% (i.e. ~100) enrollees per year are expected to donate their brains and body tissues and have comprehensive NACC-shared neuropathological assessments

**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 and ADRD, along with that of the aging mind and brain:

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, and gene expression data for the field, including what we predict will be an invaluable resource of DNA sequencing, laser-capture micro-dissected, and single nucleus 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.

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 >400,000 participants in the MindCrowd project (www.mindcrowd.org), and the largest resource of privacy-protected longitudinal electronic health record (I) data and biological samples from under-represented groups 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 genetic risk. They introduced new research paradigms, image-analysis techniques, and other approaches to help in this endeavor. Their work anticipated and advanced the conceptualization of preclinical AD.

5. They have provided invaluable resources of data, biological samples, and volunteers in persons at three levels of genetic risk for AD (i.e., with two, one and no copies of the relatively harmful APOE4 allele) and they have begun to extend this effort to persons at six levels of genetic risk (including those with one or two copies of the relatively protective APOE2 allele) and support the study of persons who remain cognitively unimpaired at older ages despite their genetic risk.

6. 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, conducted pioneering studies of preclinical AD and recently completed the world's first AD prevention trial. They have begun to provide invaluable resources of data and biological samples to advance the preclinical study and prevention of AD.

7. 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.

8. They have played leadership roles in the development, validation and use of brain imaging methods, image-analysis tools and emerging BBBMs in the unusually early detection, tracking, study, and diagnosis of AD and the evaluation of AD-modifying and prevention therapies. They have also begun to develop resources and tools to support the development of promising CSF assays, blood tests, and mobile technologies as soon as possible.

9. They and their collaborators have played leadership roles in the study of chronic traumatic encephalopathy (CTE) through "DIAGNOSE CTE", a national NINDS-sponsored longitudinal study which aims to characterize clinical, cognitive, PET, CSF, neuropathological, and BBBM changes in National Football League (NFL) players, college football players, and normal control participants who deny significant participation in contact sports, providing a shared resource of data and biological samples for the field. This year, they and their national colleagues received a new $15M grant for the next national DIAGNOSE CTE study.

10. 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. As previously noted, they have begun to incorporate ante-mortem biomarkers and new post-mortem brain tissue resources to help researchers address their goals with even greater impact.

11. They have begun to show the promise of BBBMs in the early detection, tracking, study, and diagnosis of AD and the evaluation of AD-modifying and prevention therapies. They continue to acquire and provide a shared resource of annual blood samples to support the neuropathological validation and head-to-head comparison of these and other biomarkers of AD and ADRD, and they used this shared resource to support the generalizability of these tests to under-represented Hispanic/Latino and American Indian groups. They believe that BBBMs have the potential to transform AD/ADRD research, treatment development, and clinical care, and galvanize the inclusion of persons from under-served and under-represented groups. As previously noted, with the recruitment of Nicholas Ashton, and several new investments, grants, and initiatives underway, they are poised to become one of the top fluid biomarker research programs in the world. His Biomarker discovery and assessment laboratories will become a destination center for the advancement of this research using either venous blood samples or home tests from a drop of blood.

12. Consortium researchers and their colleagues continue to characterize cognitive, biomarker, neuropathological, and other effects of COVID-19 infection in living persons and expired brain donors, and they will continue play important roles in the national effort to characterize and provide care for these long-term brain and body effects (also known as "Long COVID" or "post-acute sequelae SARS-CoV-2 infection [PASC]").

13. Led by Arizona researchers, the Alzheimer's Prevention Initiative (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 in cognitively unimpaired persons who, based on their genetic background and age or biomarker evidence of AD, are at increased risk for the clinical onset of the disease, and co-led a growing number of AD prevention trials. API introduced the first NIH-supported prevention trial of a putative disease-modifying drug therapy, showed that prevention trials were possible, and found ways to value research participants, including those from vulnerable populations in developing countries as partners in this endeavor, and it has co-led a growing number of potentially groundbreaking trials since then, with support from industry, NIH, and philanthropy. 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.

14. Thanks to exciting developments in the past year, some of which are discussed later, API now has a realistic chance to help find and support the approval and availability of the first "secondary AD prevention therapies" in cognitively unimpaired persons with blood-test evidence of amyloid plaques within the next three years—and the first "primary prevention therapies" in cognitively unimpaired persons at known genetic risk, starting before blood test evidence of amyloid plaques within the next five years.

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 capitalize on their ADRC Cores, shared resources and other collaborations to assist in this effort. Furthermore, they continue to conduct state-supported collaborative research studies to advance new ideas, identify those that have the greatest impact, and generate new findings and publications in the highest profile medical and scientific journals, and competitive grants and contracts for the study of AD, ADRD, and the aging brain. They continue to make major contributions to AD research, and they have generated the resources and collaborations needed to recruit and support a growing number of researchers and trainees to our participating institutions.

**New Developments, Opportunities and Initiatives**

Clinically effective amyloid plaque-clearing antibody therapies. In definitive clinical trials, the amyloid plaque-clearing antibody therapies lecanemab and donanemab dramatically reduced biomarker measurements of amyloid plaques and incompletely slowed down clinical decline in mildly impaired persons with biomarker evidence of AD. In addition to the implications for patients who may be eligible for treatment, these findings provide compelling support for the role of amyloid aggregates in the development, treatment and potential prevention of AD. Furthermore, they support the possibility that a treatment's effects on PET and BBBM of amyloid plaques are "reasonably likely" to predict a clinical benefit. Ongoing prevention trials of donanemab (co-led by API and Lilly) and lecanemab (co-led by Eisai and researchers from Harvard and USC) in cognitively unimpaired persons with PET or BBBM evidence of plaques now have a realistic chance to find and support the accelerated approval of these secondary prevention therapies within the next three years. API is working with Lilly on the upcoming initiation of a secondary prevention therapy of a more widely accessible secondary prevention therapy (a potentially self-administered subcutaneous plaque-reducing antibody therapy) in unimpaired persons with biomarker evidence of AD and a primary prevention therapy of the infrequently administered subcutaneous therapy in older adult APOE4 carriers without blood test evidence of AD. The goal is to find and support approval of the first secondary prevention therapy within 2 years, a more widely accessible secondary prevention therapy soon after, and a primary prevention therapy within 4-5 years. API also plans to hold a 2-day symposium in Washington, DC, to help pave a path to the approval, coverage and widespread accessibility of the first effective secondary and primary Alzheimer's prevention drug therapies within the next 2-5 Years. API's new $75M grant will clarify the ability of a plaque-reducing antibody therapy to clear plaques in ADAD and then compare three different strategies (continued treatment, a novel drug therapy known as a gamma-secretase inhibitor, or placebo) with regular monitoring in terms of their ability to avert the resumption of biomarker changes associated with AD.

Other developing medical and non-medical treatments. Researchers continue to work on developing other promising drugs for the treatment and prevention of AD, including a small number of treatments that are now in clinical trials. The investigational drugs have sought to target some of the pathophysiological processes involved in the development of amyloid aggregates, potentially damaging or beneficial neuroinflammatory changes, the phosphorylation, aggregation, and cell-to-cell transmission of tau, neuronal injury and degeneration, APOE, and other factors involved in the predisposition to and protection from AD. They include small molecules, antibody and vaccine therapies, and reversible and irreversible gene therapies, and potentially repurposed

drugs. With the advent of partially but incompletely effective plaque-clearing drugs, new paradigms will be needed to find combination or sequential treatments that could have a more profound therapeutic impact after the disease is already extensive. In the meantime, numerous studies continue to characterize the impact of health-promoting medical management, healthy diets, and lifestyle interventions on age-related cognitive decline, and the biomarkers to which they are related. Arizona researchers are actively involved in the development and evaluation of these promising treatments, including the use of “theragnostic” biomarkers to help find effective disease-modifying and prevention therapies as quickly and efficiently as possible.

Blood tests. Researchers continue to make progress in the development of biomarkers, for the assessment of amyloid plaques, tau tangles, and the diagnosis of AD, neuroinflammation, and neurodegeneration, and they are actively seeking to find biomarkers for the other pathophysiological changes (e.g., alpha-synuclein and TDP43 pathology) associated with other forms of cognitive decline. Emerging blood tests could have a profound impact on AD/ADRD research, treatment and prevention trials, and clinical care—including the ability to study extremely large populations, capitalize on legacy blood samples from observational studies and clinical trials, and support the participation of under-under-represented groups. As previously noted, Arizona researchers continue to develop go-to resources of data and blood samples to characterize and compare these BBBMs and support the accuracy and use of some of these biomarkers in under-represented Latino/Hispanic and American Indian groups.

Brain aging research. Arizona researchers continue to play leadership roles in the study of the normal aging brain and the promotion of cognitive health at older ages. This effort is reflected by the University of Arizona’s McKnight Research Institute, a wide range of studies in unimpaired older and younger adults, non-human primates, laboratory rodents, and other models, as well as studies of aging in the MindCrowd Study, promising drug development efforts, and a new $60M NIH grant, entitled "Precision Aging Network: Closing the Gap Between Cognitive Healthspan and Human LifeSpan.” This grant seeks to clarify how and why people experience brain aging differently, with the ultimate goal of developing more effective treatments and interventions targeted to the individual.

Dramatically increasing the value of our cohorts. While Arizona follows several important research cohorts in longitudinal studies and prevention trials, the value of these studies would be dramatically increased by the incorporation of biomarkers, CSF samples, and blood samples to characterize amyloid, tau, neurodegenerative and cerebrovascular disease burden, and, when available, ADRD (e.g., alpha-synuclein and TDP-43) pathologies. Arizona researchers have launched several research projects to address this challenge and have a major impact.

Increasing the study of Arizona’s under-represented American Indian and Hispanic/Latino research participants. We continue to explore ways in which to increase participation of these research participants in our ADRC Clinical Core and other research programs. We have begun to capitalize on interactions with the Strong Heart Stroke Study and University of Washington AD Center American Indian Satellite Core, to contribute to the acquisition of genetic and MRI data, the analysis of brain imaging, other biomarker, and cognitive data, and the mentorship of young investigators. We are working with (and play a leadership role in) the UA-Banner All of Us Research Program, which has already enrolled >50,000 persons, 75% of whom are from under-represented groups. Arizona researchers have been working to provide a shared resource of blood samples and privacy-protected data, amyloid and tau PET scans, and blood samples from American Indian, Hispanic/Latino, and Non-Hispanic participants, such that research can compare promising BBBMs of amyloid plaque deposition and amyloid-mediated tau tangle burden using amyloid and tau PET scans as “standards of truth.” In the meantime, they have been working with American Indian leaders to establish a local advisory group and support the acquisition and sharing of data and biological samples in ways that advance the fight against AD that are culturally sensitive and adhere to Indigenous data sovereignty principles.

COVID-19. Like other researchers, clinicians, and organizations around the world, we continue to find ways to adapt and learn from the Pandemic, find new ways to conduct our work, and advance the fight against AD, ADRD, and cognitive aging. We also continue to play important roles in the effort to characterize the long-term clinical, cognitive, biomarker and neuropathological effects of COVID through NIH's RECOVER Initiative and several investigator-initiated NIH-supported research studies.

Developing researchers, clinicians, and the next generation of leaders in the fight against AD. We have a growing number of programs to recruit, retain and support the career development of researchers, clinicians, and leaders in the field, including those from diverse backgrounds. Our programs include NIH-supported AD/ADRD-related post-doctoral and pre-doctoral research training programs, support for competitive developmental and pilot project programs, and numerous collaborative studies in the Arizona Alzheimer's Consortium. We have sought to conduct a highly innovative collaborative training and research program for promising new investigators and more senior investigators who are new to the field, and we have sought to support their participation in collaborative research programs that leverage methodological advancements and their applications in highly impactful ways. In the meantime, we continue to attract some of the best researchers, trainees, and students to Arizona, and capitalize on a growing number of exciting opportunities in the effort to achieve our ambitious goals.

**Looking Ahead**

As we stated last year, we will continue to recruit, retain, and support the development of talented researchers and clinicians, including from diverse personal and professional backgrounds, and help to establish the next generation of leaders in the fight against AD/ADRD. We will continue to reach out beyond our own disciplines and organizations, foster push-pull relationships between methodological developments and their applications, and between basic science and clinical research to address important problems in more impactful ways than any of us can do on our own. We will continue to develop and extensively share our resources. 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 include those from under-represented groups.

We will continue to play pioneering roles in the unusually early detection, tracking, and study of AD, the discovery of new treatments, and the evaluation of AD-modifying, symptomatic, and prevention therapies, and the study and management of brain aging. We will continue to develop and use research methods, experimental paradigms, and shared scientific resources to address our goals with greater power. We will place special emphases on the development, evaluation, and impactful use of BBBM and other biomarkers.

We will continue to support the development, testing and comparison of BBBMs for AD and ADRD and use them in innovative ways to help transform AD research, treatment development, and care and support the inclusion of research participants, patients and families from under-represented and under-served groups. We will continue to capitalize on multi-omics measurements in the post-mortem human brain, electronic health records and other big data, BBBM endophenotypes, artificial intelligence, machine learning, and other big data analysis methods, as well as complementary experimental studies to clarify AD/ADRD networks, drivers, and risk and protective factors and to provide targets for the discovery and development of new AD-modifying drug treatments.

The field continues to make progress in the development of gene-silencing and editing therapies and the mechanisms needed to deliver them to the right brain cells. It has also begun to develop treatments that target APOE. We are excited about the chance to put them to test with greater speed and statistical power in early phase trials. We are also excited about the chance to find combination and sequential therapies for AD and ADRD.

As we anticipated last year, we now have a remarkable chance to capitalize on recently established disease-modifying therapies, find and support the use of biomarker endpoints that are reasonably likely to be associated with a clinical benefit to inform the evaluation of medical and non-medical treatments, and accelerate the evaluation, approval, accessibility, and affordability of AD prevention therapies. Indeed, we now have a realistic chance to find and support the approval of the first effective AD prevention therapies in 2025.

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**

**25th Annual Scientific Conference – Thursday, September 12, 2024**

**Barrow Neurological Institute (Host Institution)**

**Arizona State University**

**Memorial Union**

**301 E Orange St., Tempe, AZ 85281**

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**8:15 – 9:25 AM** **POSTER PRESENTATION SET-UP & CONTINENTAL BREAKFAST**

**9:25 – 9:40AM** **WELCOME**
Michael T. Lawton, MD
Professor & Chairman, Department of Neurological Surgery
President & CEO, Barrow Neurological Institute
Chief of Vascular & Skull Base Neurosurgery

**9:40 – 10:00AM** **INTRODUCTION**
Eric M. Reiman, MD
CEO, Banner Research
Director, Arizona Alzheimer's Consortium

**10:00 – 11:15AM** **LEON THAL MEMORIAL LECTURE**
**Diagnosis, treatment, and prevention of Alzheimer's disease: Perspective from the Alzheimer's Disease Neuroimaging Initiative**

Michael Weiner, MD
Professor Emeritus in Radiology & Biomedical Imaging, Medicine, Psychiatry, and Neurology
University of California, San Francisco

Principal Investigator
Alzheimer's Disease Neuroimaging Initiative

**11:15 – 12:30PM** **ORAL RESEARCH PRESENTATIONS – SESSION I**

*12:30PM* *Student Group Photo – Arizona Ballroom*

**12:30 – 1:45PM** **POSTER SESSION I & LUNCH**

**1:45 – 3:00PM** **POSTER SESSION II & LUNCH**

**3:00 – 4:15PM** **ORAL RESEARCH PRESENTATIONS – SESSION II**

**4:15 – 4:30PM** **CLOSING REMARKS**
Eric M. Reiman, MD

**Arizona Alzheimer's Consortium**
**25th Annual Scientific Conference**

## Oral Research Presentations

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

11:15 – 11:27 AM **Recent advances and clinical implementation of blood biomarkers.** Presenting Author: Nicholas Ashton, PhD; Banner Sun Health Research Institute, Banner Alzheimer's Institute.

11:28 – 11:40 AM **Contribution of astrocytic SPARCL1 to cortical synaptic dysfunction in C9ORF72-FTD/ALS**. Presenting Author: Robert Culibrk, PhD; Barrow Neurological Institute.

11:41 – 11:53 AM **Alzheimer's disease-associated CD83(+) microglia are linked with increased immunoglobulin G4 and human cytomegalovirus in the gut, vagal nerve, and brain**. Presenting Author: Benjamin Readhead, MBBS; Arizona State University.

11:54 – 12:06 PM **Association of sleep behaviors with cerebral white matter hyperintensity volume in healthy middle-aged to older adults.** Presenting Author: Madeline Ally, MA; University of Arizona.

12:07 – 12:19 PM **Development and testing of highly scalable approaches for disclosing Alzheimer's genetic and biomarker test results.** Presenting Author: Jessica Langbaum, PhD; Banner Alzheimer's Institute.

## Oral Research Presentations

**SESSION II Moderators: Zaven Khatchaturian, PhD, & Heather Bimonte-Nelson, PhD**

3:00 – 3:12 PM **APOE, ABCA7, and RASGEF1C are associated with earlier onset of amyloid deposition from over 4000 harmonized positron emission tomography images.** Presenting Author: Mary Ellen Koran, MD, PhD; Mayo Clinic Arizona.

3:13 – 3:25 PM **DYR533: A novel DYRK1A inhibitor and its therapeutic potential in Alzheimer's disease and related tauopathies.** Presenting Author: Samantha Bartholomew; Arizona State University.

3:26 – 3:38 PM **Asymptomatic extracranial carotid atherosclerosis is associated with poorer cognitive function and reductions in white matter volume and perfusion.** Presenting Author: Summan Zahra, MBBS; University of Arizona.

3:39 – 3:51 PM **Development of a composite score to predict Lewy body pathology burden.** Presenting Author: Parichita Choudhury, MD; Banner Sun Health Research Institute.

3:52 – 4:04 PM **Development and deployment of a mobile neuroimaging laboratory for the study of age-related changes in residents of rural Arizona zip codes.** Presenting Author: Matthew Huentelman, PhD; Translational Genomics Research Institute.

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## Student Poster Presentations

1. **CORTICOSTERONE DISRUPTS SPATIAL WORKING MEMORY DURING RETENTION TESTING WHEN HIGHLY TAXED, WHICH POSITIVELY CORRELATES WITH DEPRESSIVE-LIKE BEHAVIOR IN MIDDLE-AGED, OVARIECTOMIZED FEMALE RATS.** Acuña AM, Peay DN, Whittaker K, Donnay ME, Conrad CD. Arizona State University; Arizona Alzheimer's Consortium.

2. **ASSOCIATION OF SLEEP BEHAVIORS WITH CEREBRAL WHITE MATTER HYPERINTENSITY VOLUME IN HEALTHY MIDDLE-AGED TO OLDER ADULTS.** Ally M, Aslan DH, Sayre MK, Bharadwaj PK, Maltagliati S, Lai MHC, Wilcox RR, Klimentidis YC, Raichlen DA, Alexander GE. University of Arizona; University of Southern California; Arizona Alzheimer's Consortium.

3. **SUPPORTIVE ENVIRONMENT FOR AGING: EXPLORING THE IMPACT OF MULTISENSORY ENVIRONMENTS ON SLEEP, MOOD, AND STRESS IN OLDER ADULTS WITH BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA.** Alrahyani M, Yeom D, Guest A, Lesselyong J, Fani M, Sharp N. Arizona State University; Qassim University; ViewPoint Senior Care; Arizona Alzheimer's Consortium.

4. **LOCATING YOUR NEXT DESTINATION ACROSS PROGRESSIVE MEMORY LOADS: DO SURGICAL MENOPAUSE VARIANTS IMPACT SPATIAL PRECISION?** Anyigbo K, Doyle RT, Oevermann MW, Kelley-Wolfe K, Badhwar N, Roorkeewal G, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.

5. **AN ENHANCED COGNITIVE COMPOSITE TEST SCORE WITH THE SENSITIVITY TO PREDICT AND MONITOR PROGRESSION IN THE WORLD'S LARGEST AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE KINDRED.** Badhwar N, Ghisays V, Malek-Ahmadi MH, Li S, Su Y, Reiman EM. Arizona State University; Banner Alzheimer's Institute; Mayo Clinic; Translational Genomics Research Institute; University of Arizona; Arizona Alzheimer's Consortium.

6. **DYR533: A NOVEL DYRK1A INHIBITOR AND ITS THERAPEUTIC POTENTIAL IN ALZHEIMER'S DISEASE AND RELATED TAUOPATHIES.** Bartholomew S, Winslow W, Shaw Y, Rokey S, Foley C, Hulme C, Dunckley T, Velazquez R. Arizona State University; University of Arizona; Arizona Alzheimer's Consortium.

7. **EFFICACY OF MUSIC INTERVENTIONS FOR PERSONS LIVING WITH DEMENTIA ON ACTIVITIES OF DAILY LIVING**. Bentien K, Beck A, Turner T. Midwestern University.

8. **MEASURING CEREBRAL WHITE MATTER CHANGES IN ALZHEIMER'S DISEASE USING THE AMYLOID PET TRACER FLORBETAPIR.** Bhargava V, Luo J, Devadas V, Malek-Ahmadi M, Chen K, Reiman EM, Su Y. University of Arizona, College of Medicine-Phoenix; Banner Alzheimer's Institute; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

9. **GENOTYPIC EFFECT ON MICROBIOME COMPOSITION IN A DROSOPHILA MELANOGASTER MODEL OF PARKINSON'S DISEASE.** Bonnette PE, Olson SC, Chagolla SM, Pearman K, Zhu H, Ludington WB, Call GB. Midwestern University; Carnegie Institution for Science; Johns Hopkins University; Arizona Alzheimer's Consortium.

10. **ENHANCING ALZHEIMER'S DIAGNOSIS: LEVERAGING ANATOMICAL LANDMARKS IN GRAPH CONVOLUTIONAL NEURAL NETWORKS ON HIPPOCAMPAL TETRAHEDRAL MESHES.** Chen Y, Su Y, Farazi M, Yang Z, Fan Y, George J, Wang Y. Arizona State University; Banner Alzheimer's Institute; Amazon AGI.

11. **PLASMA CYCLEGAN: INTEGRATING BLOOD-BASED BIOMARKERS FOR CROSS-MODALITY TRANSLATION FROM MRI TO PET.** Chen Y, Su Y, Fu Y, Chen K, Weidman D, Caselli RJ, Reiman EM, Wang Y. Arizona State University; Banner Alzheimer's Institute, Phoenix; Zhejiang University; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

12. **EXAMINING SEX-RELATED COGNITIVE AND NEURAL DIFFERENCES IN JUVENILE AND MIDDLE-AGED MICE IN A PAIRWISE VISUAL DISCRIMINATION TASK.** Christiansen K, Truong V, Bowser S, Lyle T, Bimonte-Nelson H, Verpeut J. Arizona State University; Arizona Alzheimer's Consortium.

13. **SEX DIFFERENCES FOR TRAJECTORIES OF PLASMA-NFL AND MRI REGION OF INTEREST CHANGE IN COGNITIVELY UNIMPAIRED LATE-MIDDLE-AGED AND OLDER ADULTS.** Clyde C, Malek-Ahmadi M, Su Y, Ghisays V, Luo J, Devadas V, Chen Y, Lee W, Protas H, Chen K, Zetterberg H, Blennow K, Caselli RJ, Reiman EM. Dine College, Tsaile, AZ; Banner Alzheimer's Institute, Phoenix; Arizona State University; University of Gothenburg; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

14. **MUSIC DURING MEALTIME IN RESIDENTIAL SETTINGS: CAREGIVER EXPERIENCES AND PERSPECTIVES.** Colussi K, Venkatesh M. A.T. Still University.

15. **EFFICIENT DIFFUSION MRI MEASUREMENTS OF TISSUE MICROSTRUCTURE WITH SPHERICAL AND PLANER TENSOR ENCODING.** Comrie CJ, Galons JP, Beach TG, Serrano GE, Hutchinson EB. University of Arizona; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

16. **CNS-ACTIVE DRUGS FOR NEUROPSYCHIATRIC DISORDERS DIFFERENTIALLY MODULATE RISK OF AD DEVELOPMENT.** Cortes-Flores H, Torrandell-Haro G, Diaz Brinton R. University of Arizona; Arizona Alzheimer's Consortium.

17. **TDP-43 SEVERITY IS NOT ASSOCIATED WITH COGNITIVE DOMAIN DISPERSION IN COGNITIVELY UNIMPAIRED AND MILD COGNITIVE IMPAIRMENT AUTOPSY CASES.** Crosby S, Malek-Ahmadi M, Perez SE, Mufson EJ. University of Arizona; Banner Alzheimer's Institute; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

18. **THE SYNTHESIS OF NEUROMODULATORY MOLECULES BY A GUT MICROBIAL GLUTAMATE DECARBOXYLASE: GABA, TAURINE AND ITS ANALOGS, AND B-ALANINE.** Dadi P, Pauling CW, Shrivastava A, Shah DD. Arizona State University; Arizona Alzheimer's Consortium.

19. **THE ORAL TRAIL MAKING TEST: NORMATIVE ANALYSIS FOR OLDER ADULTS**. Dessert A, Malek-Ahmadi MH, Blake L, Auman B, Belden C, Atri A, Arce R, Serrano G. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Midwestern University; Arizona Alzheimer's Consortium.

20. **A NOVEL APPROACH FOR DETECTING AGE-RELATED CHANGES IN THE EX-VIVO FEMALE BONNET MACAQUE BRAIN USING MULTI-PARAMETRIC MRI.** Dieckhaus L, McDermott K, Gray DT, Barnes CA, Hutchinson EB. University of Arizona; University of California, Los Angeles; Arizona Alzheimer's Consortium.

21. **INVESTIGATING THE EFFECTS OF ORALLY ADMINISTERED BACTEROIDES FRAGILIS ON MICE MODELING ALZHEIMER'S DISEASE PATHOLOGIES.** Dikshit S, Conn K, Barroso-Montalvo D, Monarrez DV, Finkle H, Caporaso G, Cope EK. Northern Arizona University; Arizona Alzheimer's Consortium.

22. **END-TO-END 3D CYCLEGAN MODEL FOR AMYLOID PET HARMONIZATION.** Dong X, Shah J, Ghisays V, Luo J, Chen Y, Lee W, Li B, Wu T, Reiman EM, Chen K, Wang Y, Su Y. Arizona State University; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

23. **END-TO-END 3D CYCLEGAN MODEL FOR MRI HARMONIZATION.** Dong X, Shah J, Ghisays V, Luo J, Chen Y, Lee W, Li B, Wu T, Reiman EM, Chen K, Wang Y, Su Y. Arizona State University; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

24. **EXPLORING SURGICAL MENOPAUSE EFFECTS ON RAT FOREBRAIN CHOLINERGIC CIRCUITS: IMPLICATIONS FOR THE ENDOCRINE-BRAIN INTERFACE**. Doyle RT, Pastor J, Balasubramanian KS, Verpeut J, Bimonte-Nelson HA, Newbern JM. Arizona State University; Arizona Alzheimer's Consortium.

25. **A CNN-BASED FOUNDATION MODEL FOR EARLY DETECTION OF PRE-SYMPTOMATIC ALZHEIMER'S DISEASE**. Dumitrascu OM, Li X, Youssef A, Sobczak J, Zhu W, Saxena S, Woodruff BK, Caselli R, Wang Y. Mayo Clinic Arizona; Arizona State University; Arizona Alzheimer's Consortium.

26. **SELF-SUPERVISED LEARNING FOR ALZHEIMER'S DISEASE DETECTION USING COLOR FUNDUS PHOTOGRAPHY**. Dumitrascu OM, Li X, Zhu W, Woodruff BK, Nikolova S, Sobczak J, Youssef A, Saxena S, Andreev J, Caselli R, Chen JJ, Wang Y. Mayo Clinic Arizona; Arizona State University; Mayo Clinic Rochester; Arizona Alzheimer's Consortium.

27. **ENDOTHELIAL ACTIVATION IS ASSOCIATED WITH HIPPOCAMPAL ATROPHY IN PARTICIPANTS WITH ASYMPTOMATIC EXTRACRANIAL CAROTID ARTERY DISEASE.** French SR, Zahra S, Wiskoski HE, Arias JC, Khakwani KZR, Howell C, Escareno CE, Heitkamp EN, Vazquez F, Pugazhendhi A, Ally M, Culwell GC, Vitali F, Bedrick EJ, Trouard TP, Alexander GE, Weinkauf CC. University of Arizona; Arizona Alzheimer's Consortium.

28. **PARKINSON'S-LINKED BRAIN FEATURES IN AGING AUTISTIC ADULTS.** Galindo MV, Valdez M, Ofori E, Peterson D, Rodi A, Braden BB. Arizona State University; Arizona Alzheimer's Consortium.

29. **ADMINISTRATION OF ISOFORM-SELECTIVE INHIBITOR OF HEAT SHOCK PROTEIN 90-BETA AMELIORATES MEMORY LOSS AND NOCICEPTIVE BEHAVIOR IN 8-MONTH-OLD 5XFAD MICE**. Gratreak BDK, Seekins CA, Serwetnyk S, D'Amico T, Blagg BS, Streicher JM. University of Arizona; University of Notre Dame; Arizona Alzheimer's Consortium.

30. **CONTINUAL SKILL AND TASK LEARNING VIA DIALOGUE**. Gu W, Kondepudi N, Huang L, Gopalan N. Arizona State University; Arizona Alzheimer's Consortium.

31. **CARDIOMETABOLIC RISK MEDIATES THE ASSOCIATION BETWEEN PERCEIVED STRESS AND EPISODIC MEMORY SIMILARLY AMONG HISPANIC/LATINO AND NON-HISPANIC WHITE INDIVIDUALS**. Guareña L, Huentelman MJ, Ryan L. University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

32. **IDENTIFYING COGNITIVE SUBGROUPS IN OLDER ADULTS FROM COMMUNITY DATA VIA HIERARCHICAL CLUSTER ANALYSIS.** Hall JD, Green J, Chou Y. University of Arizona; Arizona Alzheimer's Consortium.

33. **TREATMENT WITH PSILOCYBIN ALLEVIATES APPROACH-AVOIDANCE BEHAVIOR IN AGED MICE.** Hanson T, Lifshitz D, Law O, Hays A, Flores B, Olive MF, Mennenga SE, Lewis CR. Arizona State University; University of Arizona, College of Medicine-Phoenix; Arizona Alzheimer's Consortium.

34. **ALZHEIMER'S DISEASE GENETIC RISK DOSAGE IN AUTISTIC INDIVIDUALS.** Harker SA, Piras I, Huentelman MJ, Taguinod F, Lewis CR, Braden BB. Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

35. **A NOVEL SCORING PROTOCOL FOR ASSESSING UNPROMPTED IMAGINATIVE THINKING IN YOUNG AND OLDER ADULTS.** Hovhannisyan M, Grilli MD, Andrews-Hanna JR. University of Arizona; Arizona Alzheimer's Consortium.

36. **PERFUSION AND CEREBROVASCULAR REACTIVITY CHARACTERIZATION IN ALZHEIMER'S DISEASE AND VASCULAR DEMENTIA.** Keeling EG, McElvogue MM, Ott LR, Burke AD, Sabbagh MN, Bakkar N, Stokes AM. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.

37. **AGE AND APOE ASSOCIATED TRAJECTORIES FOR PLASMA-NFL AND CORTICAL THICKNESS IN PRE-CLINICAL ALZHEIMER'S DISEASE.** Kira K, Malek-Ahmadi M, Su Y, Ghisays V, Luo J, Devadas V, Chen Y, Lee W, Protas H, Chen K, Zetterberg H, Blennow K, Caselli RJ, Reiman EM. Arizona State University; Banner Alzheimer's Institute; University of Gothenburg; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

38. **THE ROLE OF CARDIOVASCULAR BURDEN ON EXECUTIVE FUNCTIONING AND PROCESSING SPEED PERFORMANCE IN A COGNITIVELY NORMAL SAMPLE.** Krall D, Malek-Ahmadi M, Blake L, Auman B, Belden CM, Atri A, Arch R, Serrano G. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

39. **CHARACTERIZATION OF ALZHEIMER'S DISEASE-RELATED NEURO-INFLAMMATION UTILIZING A 5XFAD MOUSE MODEL.** Leslie A, Reyes-Reyes E, Rodgers K. University of Arizona; Arizona Alzheimer's Consortium.

40. **TREATMENT WITH PSILOCYBIN ALLEVIATES APPROACH-AVOIDANCE BEHAVIOR IN AGED MICE.** Lifshitz D, Hanson T, Law O, Hays A, Flores B, Olive MF, Mennenga* SE, Lewis* CR. Arizona State University; Arizona Alzheimer's Consortium.

41. **RISK FACTORS ASSOCIATED WITH MILD COGNITIVE IMPAIRMENT AMONG MEXICAN IMMIGRANT ADULTS IN SOUTHERN ARIZONA**. Lindemer SL, Maldonado A, Ochoa Mora E, Gonzalez AS, Villavicencio EA, Garcia DO. University of Arizona; Arizona Alzheimer's Consortium.

42. **A NOVEL PRECLINICAL TASK FOR THE ASSESSMENT OF SOCIAL RECOGNITION MEMORY UNDER VARIOUS LOAD DEMANDS.** Lizik CR, Kelley-Wolfe K, Wu ES, Asadifar S, Verpeut J, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.

43. **CREATION AND TESTING OF A NOVEL FINE MOTOR TASK INTENDED FOR THE DETECTION AND ANALYSIS OF NEURODEGENERATIVE PRECURSORS.** Lukacik D, Melick A, Schaefer S, Beeman S, Verpeut JL. Arizona State University; Arizona Alzheimer's Consortium.

44. **A NEUROVASCULAR UNIT ON-A-CHIP MODEL FOR STUDYING THE INTERACTIONS BETWEEN BRAIN CAPILLARY NICHE AND STEM CELL-DERIVED NEURONS**. Manoharan TJM, Bamfonga G, Andrews MG, Migrino RQ, Nikkhah M. Arizona State University; Phoenix Veterans Affairs Health Care System; University of Arizona, College of Medicine-Phoenix; Arizona Alzheimer's Consortium.

45. **LYSOSOMAL DYSFUNCTION PROMOTES MICROGLIAL MEDIATED INFLAMMATION AND REDUCTION IN PGRN LEVELS.** Maqsood S, Lin J, Harrison AM, Uppalapati CK, Leyva KJ, Hull EE. Midwestern University; Arizona Alzheimer's Consortium.

46. **HIGH RESOLUTION EX VIVO MRI REVEALS AGE-RELATED CHANGES IN BONNET MACAQUE LOCUS COERULEUS ASCENDING WHITE MATTER TRACTS.** McDermott K, Dieckhaus L, Hutchinson E B, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

47. **BEHAVIORAL AND METABOLIC PROFILES IN AN AGED, HUMANIZED APP/APOE MOUSE MODEL OF ALZHEIMER'S DISEASE RISK.** McLean JW, Bhattrai A, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.

48. **NOVEL FINE MOTOR TASK FOR STUDYING KINEMATICS IN THE TGF344-AD RAT MODEL: APPLICATIONS OF NOVEL MACHINE LEARNING TECHNIQUES IN NEUROSCIENCE.** Melick A, Lukacik D, Bimonte-Nelson H, Schaefer S, Beeman S, Verpeut JL. Arizona State University; Arizona Alzheimer's Consortium.

49. **EXTENDED EXPOSURE TO ALZHEIMER'S RISK FACTORS INCREASES ALZHEIMER'S DIAGNOSIS RISK, AMPLIFIED IN APOE4 CARRIERS: IMPLICATION FOR DELAYED ONSET OF ALZHEIMER'S RISK FACTORS.** Merlini S, Vitali F, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.

50. **NUCLEAR EXPORT OF TDP-43 IS FACILITATED BY ADAR2-MEDIATED RNA EDITING.** Moore S, Julian D, Lorenzini I, McMillan M, Alsop E, Macklin-Isquierdo S, Lehmkuhl E, Kalab P, Hayes L, Zarnescu D, Van-Keuren Jensen K, Barmada S, Sattler R. Barrow Neurological Institute; University of Arizona, College of Medicine-Phoenix; University of Michigan; Translational Genomics Research Institute; University of Arizona; Johns Hopkins University, School of Medicine; Penn State, College of Medicine; Arizona Alzheimer's Consortium.

51. **INCREASED GLUCOSE AND CA4 VOLUME INTERACT TO PROMOTE HIPPOCAMPAL MEMORY FUNCTION IN OLDER ADULTS.** Norman SL, Hoscheidt S, Matijevic S, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.

52. **CHOLINERGIC MUSCARINIC ANTAGONISM ON A SPATIAL MEMORY TASK: HYSTERECTOMY WITH OVARIAN CONSERVATION YIELDS COMPARABLE IMPAIRMENTS TO OVARIAN REMOVAL IN A RAT MENOPAUSE MODEL.** Oevermann MW, Lizik CR, Wu ES, Kelley-Wolfe K, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.

53. **CORTICAL BRAIN PERFUSION AND ITS RELATIONSHIP WITH HIPPOCAMPAL-BASED TASKS IN LONG-COVID**. Palmer J, Hoscheidt S, Rhodes, A, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.

54. **APOE4 INTERACTS WITH PERIMENOPAUSAL TRANSITION IN REGULATING CENTRAL AND PERIPHERAL LIPID METABOLISM**. Pan H, Mi Y, Qi G, Wang T, Brinton RD, Yin F. University of Arizona; Arizona Alzheimer's Consortium.

55. **USING 3D ORGANOIDS TO INTERROGATE METABOLIC DYSREGULATION IN AGING & ALZHEIMER'S DISEASE.** Pennington T, Cerna S, Andrews M. Arizona State University; Arizona Alzheimer's Consortium.

56. **IMPAIRED L-TYPE VOLTAGE-GATED CA2+ CHANNEL FUNCTION IN CEREBRAL ARTERIOLAR MYOCYTES FROM HUMANIZED APOε4 KNOCK-IN MICE.** Polk FD, DaSilva JF, Pires PW. University of Arizona; Arizona Alzheimer's Consortium.

57. **NOVEL IMAGING SIGNATURES TO DETECT ROD MICROGLIA AFTER EXPERIMENTAL DIFFUSE TRAUMATIC BRAIN INJURY.** Pressman MM, Giordano KR, Griffiths DR, Hutchinson EB, Lifshitiz J. University of Arizona, College of Medicine-Phoenix; Phoenix VA Health Care System; University of Arizona; Arizona Alzheimer's Consortium.

58. **COMPARING OLDER ADULT STRESS LEVELS ASSOCIATED WITH COGNITIVE AND MOTOR TESTING TO ADVANCE EARLIER DEMENTIA SCREENING.** Reed AM, Chacon E, Schaefer SY. Arizona State University; Arizona Alzheimer's Consortium.

59. **THE RELATIONSHIP BETWEEN PATTERN SEPARATION AND OBJECT DISCRIMINATION.** Rhodes A, Palmer J, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.

60. **AN EXAMINATION OF AGE-RELATED DIFFERENCES IN AUTOBIOGRAPHICAL THINKING USING AN EXPERIENCE SAMPLING APPROACH: INSIGHTS FROM THE MIND WINDOW APP.** Puig Rivera VA, Cervantes LJ, Freveletti D, Andrews ES, Grilli MD, Andrews-Hanna JR. University of Arizona; Arizona Alzheimer's Consortium.

61. **THE IMPACT OF DEMENTIA AND THE LIVED EXPERIENCE OF COUPLES.** Santos B, Turner T. Midwestern University.

62. **SEX-SPECIFIC HORMONE AND GENE EXPRESSION ALTERATIONS IN EXPERIMENTAL MODEL OF TRAUMATIC BRAIN INJURY**. Simmons A, Wilferd S, Pena V, Plaisier C, Bimonte-Nelson H, Sirianni R, Stabenfeldt S. Arizona State University; University of Massachusetts; Arizona Alzheimer's Consortium.

63. **IDENTIFYING SYNAPTOME ABERRATIONS IN C9ORF72 ALS/FTD PATIENT-DERIVED CORTICAL NEURONS.** Spillman A, Bustos L, Hansen N, Garcia-Mansfield K, Gittings L, Alsop E, Van Keuren-Jensen K, Pirrotte P, Sattler R. Barrow Neurological Institute; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

64. **INVESTIGATING AGE-RELATED CHANGES OF MPFC NEURAL RESPONSES TO VENTRAL HIPPOCAMPUS STIMULATION**. Srivathsa SV, Vishwanath A, Cowen SL, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

65. **TAS2R38 SUPERTASTERS ARE ASSOCIATED WITH LOWER RISK OF ALZHEIMER'S DISEASE (AD) WITH THE ADVANCEMENT OF AGE.** Su CW, Chen K, Wang Q. Arizona State University; Arizona Alzheimer's Consortium.

66. **KNOWLEDGE OF RISK FACTORS FOR DEMENTIA AND ATTITUDES ON A DEMENTIA PREVENTION PROGRAM BY AGE AND ETHNICITY IN ARIZONA.** Talkad H, Chen Y, Bress A, Langbaum J, Tariot P, Pruzin J. University of Arizona, College of Medicine-Phoenix; Banner Alzheimer's Institute; University of Utah; Arizona Alzheimer's Consortium.

67. **ADULTHOOD DIETARY CHOLINE SUPPLEMENTATION MODESTLY LOWERS METABOLIC SYMPTOMS RELATED TO ALZHEIMER'S DISEASE RISK IN THE TS65DN MODEL OF DOWN SYNDROME.** Tallino S, Etebari R, Leon H, Sepulveda I, Nath D, Bartholomew B, Velazquez R. Arizona State University; Arizona Alzheimer's Consortium.

68. **IDENTIFYING HIGH-RISK SUBGROUPS IN ALZHEIMER'S DISEASE PATIENTS: AN ANALYSIS OF DEEP EMBEDDED CLUSTERING IN WISCONSIN REGISTRY FOR ALZHEIMER'S PREVENTION PARTICIPANTS.** Tirambulo CVG, Merlini S, Paul M, Lizarraga C, Diaz-Brinton R, Vitali F. University of Arizona; Arizona Alzheimer's Consortium.

69. **DIFFERENTIAL PREDICTION OF LEWY BODY PATHOLOGY BURDEN USING UNIVARIATE OR ML-BASED COMPOSITE NON-INVASIVE NEUROCOGNITIVE MEASURES.** Triebswetter C, Choudhury P, Zhang N, Ho A, Tremblay C, Belden C, Mehta S, Adler CH, Driver-Dunkley E, Shill H, Shprecher D, Serrano G, Beach T, Reiman E, Atri A, Chen K. University of Arizona - College of Medicine, Phoenix; Banner Sun Health Research Institute; Mayo Clinic, Arizona; Banner Alzheimer's Institute; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

70. **INTERPRETABLE DEEP LEARNING FRAMEWORK FOR UNDERSTANDING MOLECULAR CHANGES IN HUMAN BRAINS WITH ALZHEIMER'S DISEASE: IMPLICATIONS FOR MICROGLIA ACTIVATION AND SEX DIFFERENCES.** Trivedi MR, Joshi AM, Shah J, Readhead BP, Wilson MA, Su Y, Reiman EM, Wu T, Wang Q. Arizona State University; ASU-Mayo Center for Innovative Imaging; Latent AI, Inc., Princeton, NJ; Banner Alzheimer's Institute, Phoenix; Arizona Alzheimer's Consortium.

71. **AGING AND AUTISM: MODULATION OF THE CEREBELLAR NUCLEI DURING CRITICAL PERIODS OF DEVELOPMENT TO ASSESS SOCIAL CHANGES WITH AGE IN MICE.** Truong V, Lyle T, Verpeut J. Arizona State University; Arizona Alzheimer's Consortium.

72. **ACTIVITY-DEPENDENT OVEREXPRESSION OF EGR1 IN THE HIPPOCAMPUS IMPROVES CONTEXTUAL MEMORY IN MICE.** Wallace SG, Higa N, Ho WH, Campbell JM, Okuno H, Gallitano AL. University of Arizona, College of Medicine-Phoenix; Kagoshima University; Arizona Alzheimer's Consortium.

73. **UNRAVELING SEX DIFFERENCES IN ALZHEIMER'S DISEASE SUSCEPTIBILITY: INSIGHTS FROM SINGLE NUCLEUS RNA-SEQUENCING IN RHESUS MACAQUES.** Watkins KL, Yang W, Bohlen MO, O'Day DR, O'Neill MB, Cayo Biobank Research Unit, Martínez MI, Starita LM, Montague MJ, Platt ML, Chiou KL, Shendure J, Snyder-Mackler N. Arizona State University; University of Washington; Duke University; Brotman Baty Institute; Caribbean Primate Research Center; University of Puerto Rico; University of Pennsylvania; Arizona Alzheimer's Consortium.

74. **EFFECT OF ESTROGEN AND PROGESTERONE LOSS ON NEUROGENESIS-RELATED SPATIAL LEARNING AND SEARCH STRATEGIES IN AGING FEMALE RATS.** Winter GM, Corenblum MJ, Pillutla, SV, Meredith J, Wene P, Menakuru N, Cowen SL, Madhavan L. University of Arizona; Arizona Alzheimer's Consortium.

75. **EXPLORING THE RELATIONSHIP BETWEEN EXTRACRANIAL CAROTID ARTERY DISEASE SEVERITY AND CHANGES IN BRAIN CORTICAL MORPHOLOGY**. Wiskoski H, Arias J, Zahra S, Khakwani K, Do L, Pugazhendhi A, Mushtaq R, Johnson K, Altbach M, Trouard T, Weinkauf C. University of Arizona; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

76. **HIGH-RESOLUTION QUANTITATIVE T1 AND T2 MAPPING OF THE BRAIN TO ASSESS CHANGES RELATING TO EXTRACRANIAL CAROTID ARTERY DISEASE.** Wiskoski H, Johnson K, Arias J, Pugazhendhi A, Mushtaq R, Ahanonu E, Bilgin A, Trouard T, Weinkauf C, Altbach M. University of Arizona; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

77. **INFLAMMATION, BRAIN AGING, AND DEMENTIA RISK AMONG FORAGER-FARMERS IN THE BOLIVIAN AMAZON.** Aronoff JE, Jenkins CL, Garcia AR, Buetow K, Beheim B, Rodriguez DE, Gutierrez RQ, Cuata JB, Chui H, Walters EE, Mack WJ, Gatz M, Finch CE, Irimia A, Law ME, Barisano G, Cummings DK, Hooper PL, Kraft TS, Stieglitz J, Gurven MD, Kaplan H, Trumble BC. Arizona State University; Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany; Universidad de San Simón, Cochabamba, Bolivia; Tsimane Health and Life History Project, San Borja, Beni, Bolivia; University of Southern California; Monash University, Melbourne, Victoria, Australia; Stanford University; Chapman University; University of Utah; Toulouse School of Economics, Toulouse, France; University of California, Santa Barbara.

78. **BIOMARKER DISCOVERY IN ALZHEIMER'S AND NEURODEGENERATIVE DISEASES USING NUCLEIC ACID-LINKED IMMUNO-SANDWICH ASSAY.** Ashton NJ, Benedet AL, Di Molfetta G, Pola I, Anastasi F, Fernández-Lebrero A, Puig-Pijoan A, Keshavan A, Schott J, Tan K, Montoliu-Gaya L, Isaacson R, Bongianni M, Tolassi C, Cantoni V, Alberici A, Padovani A, Zanusso G, Pilotto A, Borroni B, Suárez-Calvet M, Blennow K, Hansson O, Zetterberg H. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Lund University, Lund, Sweden; Barcelonaβeta Brain Research Center (BBRC), Pasqual Maragall Foundation, Barcelona, Spain.

79. **EVALUATION OF PLASMA PHOSPHO-TAU217 FOR ALZHEIMER'S DISEASE USING A FULLY AUTOMATED PLATFORM – AN INTERNATIONAL MULTI-CENTER STUDY IN PRIMARY AND SECONDARY CARE.** Palmqvist S, Anastasi F, Warmenhoven N, Tideman P, Mattsson-Carlgren N, Smith R, Ossenkoppele R, Tan K, Dittrich A, Skoog I, Janelidze S, Stomrud E, Zetterberg H, Kern S, Pilotto A, Quaresima V, Brugnoni D, Padovani A, Puig-Pijoan A, Fernández-Lebrero A, Contador J, Blennow K, Suárez-Calvet M, Hansson O, Ashton NJ. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Lund University, Lund, Sweden; Barcelonaβeta Brain Research Center (BBRC), Pasqual Maragall Foundation, Barcelona, Spain.

80. **IS DYSREGULATION OF MYELIN, OLIGODENDROCYTE OR NEUROFILAMENT CAUSING OR INFLUENCING WHITE MATTER RAREFACTION CHANGES?** Atri T, Pastrana González S, Lorenzini I, Intorcia AJ, Wermager Z, Walker JE, Qiji S, Shull A, Krupp A, McHattie R, Cline M, Borja C, Arce R, Aslam S, Mariner M, Beach TG, Serrano GE. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

81. **SEX-SPECIFIC MOLECULAR PATHWAYS IN ALZHEIMER'S DISEASE: RESULTS FROM RNA SEQUENCING AND BIOINFORMATICS ANALYSIS.** Awong P, Walker J, Lorenzini I, Theng Beh S, Arce RA, Qiji SH, Intorcia AJ, Borja CI, Cline MP, Krupp AN, McHattie RD, Wermager ZR, Shull A, Mariner MR, Tremblay C, Beach TG, Aslam S, Serrano GE. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

82. **THE HUMAN RAP1 INCREASE GAMMA-SECRETASE ACTIVITY IN AN OXIDATIVE ENVIRONMENT.** Bae NS, Whetzel A, Lewis KA, Swanson MJ. Midwestern University; Arizona Alzheimer's Consortium.

83. **IMPACT OF SENESCENCE ON MITOCHONDRIAL DYSFUNCTION IN ALZHEIMER'S DISEASE.** Beh ST, Gulmen M, Dunckley N, Arce R, Borja C, Intorcia A, Walker J, Cline M, Qiji S, Mariner M, Krupp A, McHattie R, Wermager Z, Shull A, Tremblay C, Aslam S, Lorenzini I, Lue LF, Beach T, Serrano G. Banner Sun Health Research Institute; Boston University.

84. **ASSESSMENT OF MICROSTRUCTURAL CHANGES IN WHITE MATTER HYPERINTENSITIES IN AGING AND MILD COGNITIVE IMPAIRMENT REVEALED BY ADVANCED DIFFUSION MRI.** Bergamino M, Nelson MR, Keeling E, Stokes AM. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.

85. **A 3D CELL CULTURE AND INJURY MODEL TO STUDY NEURODEGENERATIVE EFFECTS DUE TO TRAUMATIC INJURIES.** Bjorklund G, Brafman D. Arizona State University; Arizona Alzheimer's Consortium.

86. **APOE, ABCA7, AND RASGEF1C ARE ASSOCIATED WITH EARLIER ONSET OF AMYLOID DEPOSITION FROM OVER 4000 HARMONIZED POSITRON EMISSION TOMOGRAPHY IMAGES.** Castellano T, Wang TC, Wu Y, Archer D, Janve V, Durant A, Regelson A, Cody K, Harrison T, Engelman C, Jagust W, Albert M, Johnson S, Resnick S, Sperling R, Bilgel M, Saykin A, Vardarajan B, Mayeux R, Alzheimer's Disease Neuroimaging Initiative, Betthauser T, Bennett DA, Schneider J, De Jager P, Menon V, Toson D, Mormino E, Dumitrescu L, Hohman T, Koran M. Vanderbilt University Medical Center; Stanford University; University of California, Berkeley; University of Wisconsin; Johns Hopkins University School of Medicine; University of Wisconsin School of Medicine; National Institute on Aging, National Institutes of Health; Massachusetts General Hospital; Brigham and Women's Hospital, Boston, Massachusetts; Indiana University; Columbia University Medical Center; The New York Presbyterian Hospital; Rush University Medical Center; Columbia University Irving Medical Center; University of California San Francisco; Mayo Clinic of Arizona.

87. **DEVELOPMENT OF A COMPOSITE SCORE TO PREDICT LEWY BODY PATHOLOGY BURDEN.** Choudhury P, Chen K, Zhang N, Tremblay C, Ho AH, Belden CM, Adler CH, Shill H, Mehta S, Driver-Dunckley E, Shprecher DR, Serrano GE, Beach TG, Reiman EM, Atri A. Banner Sun Health Research Institute; Arizona State University; University of Arizona; Banner Alzheimer's Institute; Mayo Clinic Arizona; Barrow Neurological Institute; Brigham and Women's Hospital; Harvard Medical School; Arizona Alzheimer's Consortium.

88. **A MIXED-METHODS, DIGITAL HEALTH APPROACH TO SUPPORTING INDIVIDUALS WITH COGNITIVE IMPAIRMENT AND FAMILY MEMBERS IN RURAL COMMUNITIES: THE NORTHERN ARIZONA MEMORY STUDY.** Cerino ES, McCoy MC, Martinez M, Seaton TJ, Goldtooth AD, Livingston RA, Dopson R, Lucero L, McCarthy MJ. Northern Arizona University; Joe C. Montoya Community & Senior Center; Arizona Alzheimer's Consortium.

89. **ACCOUNTING FOR WHITE MATTER UPTAKE IMPROVES BETWEEN TRACER AGREEMENT IN AMYLOID PET.** Chen Y, Protas H, Luo J, Li S, Esfahani MJS, Ghisays V, Lee W, Wu T, Reiman EM, Chen K. Banner Alzheimer's Institute; Arizona Alzheimer's Consortium; Arizona State University; University of Arizona; University of Arizona, College of Medicine-Phoenix.

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

91. **TRANSCRIPTIONAL CHARACTERIZATION OF RELAXIN-3-POSITIVE NEURONS IN AGING AND ALZHEIMER'S DISEASE.** de Ávila C, Nolz J, Khatri D, Uzum Z, Intorcia A J, Chee S, Serrano GE, Beach TG, Gundlach AL, Mastroeni DF. Arizona State University; Regenerative Medicine Core; Arizona Alzheimer's Consortium; Banner Sun Health Research Institute; University of Melbourne.

92. **BRAIN BARRIERS BREAKDOWN IN ALS AND ALS-FTD.** Dominick M, Alsop E, Antone J, Van-Keuren Jensen K, Bowser R, Bakkar N. Barrow Neurological Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

93. **APOE STATUS IMPACTS RETINAL ARTERIOLAR FRACTAL DIMENSION IN INDIVIDUALS WITH NORMAL COGNITION.** Dumitrascu O, Badr A, Youssef A, Graff T, Andreev J, Saxena S, Vuong M, Li X, Caselli R, Wang Y, Woodruff B. Mayo Clinic Arizona; Arizona State University; Arizona Alzheimer's Consortium.

94. **PSEUDOTIME ANALYSIS IN ALZHEIMER'S DISEASE: IDENTIFYING KEY GENES OF MOLECULAR PROGRESSION IN THE BRAIN**. Ecca F, Song S, Naymik M, Huentelman MJ, Piras IS. Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

95. **NEUROPSYCHOLOGICAL SUBTYPES IN HISPANIC NACC PARTICIPANTS.** Edmonds EC, Rapcsak SZ. Banner Alzheimer's Institute, Tucson, AZ; University of Arizona; Arizona Alzheimer's Consortium.

96. **WHAT'S IN A NAME? TERMS PERSONS SUPPORTING PEOPLE LIVING WITH MCI OR DEMENTIA USE TO DESCRIBE THEIR ROLE.** Erickson C, Clapp J, Gupta A, Kleid M, Harkins K, Stites SD, Peterson A, Karlawish J, Largent E. Banner Alzheimer's Institute; University of Pennsylvania; George Mason University.

97. **TIME RESTRICTED EATING IN ALZHEIMER'S DISEASE (TREAD): A PILOT STUDY.** Geda YE, Krell-Roesch J, Zaniletti I, Chahal G, Smith T, DeCuna CJ, Aliskevich E, Gunning J, Khan N, Eagan D, Racette SB. Barrow Neurological Institute; Karlsruhe Institute of Technology, Karlsruhe, Germany; IZ Statistics LLC, Tampa, FL; Arizona State University; Arizona Alzheimer's Consortium.

98. **IMPACT OF APOE4 DEMENTIA RISK AS A FUNCTION OF AGE IN UNDER-REPRESENTED GROUPS USING DATA FROM THE ALL OF US RESEARCH PROGRAM.** Ghisays V, Khajouei E, Piras IS, Goradia DG, Malek-Ahmadi MH, Chen Y, Naymik M, Saner D, Su Y, Huentelman MJ, Karnes JH, Reiman EM. Banner Alzheimer's Institute; University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

99. **VR AND SECONDARY FAMILY CAREGIVERS OF PEOPLE WITH ADRD: A SERIES OF FOCUS GROUPS ABOUT THEIR ROLE AND NEEDS- PRELIMINARY DATA.** Gómez-Morales A, Bahrami R. Arizona State University; Arizona Alzheimer's Consortium.

100. **INVESTIGATING OPTIC NERVE ALTERATIONS IN PARKINSON'S DISEASE: A HISTOLOGICAL AND PROTEIN ANALYSIS STUDY.** Gonzalez A, Lorenzini I, Shull A, Qiji S, Walker JE, Theng Beh S, Arce RA, Intorcia AJ, Borja CI, Cline MP, Krupp AN, McHattie RD, Wermager ZR, Mariner MR, Aslam S, Tremblay C, Beach TG, Serrano GE. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

101. **SYNAPTOSOME PROTEOMICS TO IDENTIFY MOLECULAR SIGNATURES IN DEMENTIA SPECTRUM DISORDERS.** Gopalakrishnan L, Sharma R, Martinez M, Bakkar N, Hansen N, Pirrotte P, Bowser R. Barrow Neurological Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

102. **MINISCOPE IMAGING OF MICROGLIA BEFORE AND AFTER EXPERIMENTAL HEAD INJURY.** Griffiths DR, McQueen KA, Giordano KR, Lifshitz J. University of Arizona, College of Medicine-Phoenix; Phoenix VA Health Care System; Arizona Alzheimer's Consortium.

103. **SOCIAL NETWORKS AMONG CAREGIVERS OF PERSONS LIVING WITH DEMENTIA IN ARIZONA: FINDINGS FROM YEAR 1**. Guest MA, Peckham A, Sadow S, Schuchardt-Vogt C, Pittuch K, Hook J. Arizona State University; Arizona Alzheimer's Consortium.

104. **CEREBRAL AND CAROTID ARTERIES FUNCTION IN MARFAN SYNDROME: EFFECTS OF EXERCISE TRAINING.** Gusek B, Priday C, Folk R, Vallejo-Elias J, Esfandiarei M. Midwestern University; University of Arizona.

105. **THE IMPACT OF TAU ON MITOCHONDRIAL FUNCTION ASSOCIATED WITH ALZHEIMER'S DISEASE.** Hernandez BL, Cristofano JA, Tseng J-H. Arizona State University; Arizona Alzheimer's Consortium.

106. **BEHAVIORAL AND NEURAL DISSOCIATIONS BETWEEN EPISODIC MEMORY RETRIEVAL SUCCESS AND PRECISION IN HEALTHY AGING AND MILD COGNITIVE IMPAIRMENT.** Hill PF, Markham DC, Garren JD, Ekstrom AD. University of Arizona; Arizona Alzheimer's Consortium.

107. **SPLICING AND TRANSCRIPTOMIC CHANGES IN MATRIN 3 S85C KNOCK-IN MICE.** Houchins N, Quezada G, Valentine A, Bakkar N, Bowser B, Medina DX. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

108. **METABOLIC HEALTH AND INFLAMMATORY MARKERS AS TARGETS FOR HEALTHY COGNITIVE AGING.** Hoscheidt S, Huentelman M, Ryan L. University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

109. **INTESTINAL MICROBIOTA DYSBIOSIS IN TRANSGENIC ALZHEIMER'S DISEASE MOUSE MODELS.** Jones TB, Chu P, Jones D, Jentarra G. Midwestern University; Arizona Alzheimer's Consortium.

110. **INTERROGATING THE PROTECTIVE EFFECTS OF NEURONAL RBBP7 ON NEUROINFLAMMATION, AUTOPHAGY AND TAU PATHOGENESIS.** Judd JM, Winslow W, Dave N, Velazquez R. Arizona State University; Arizona Alzheimer's Consortium; Gates Ventures.

111. **CHARACTERIZING THE GENETIC EXPRESSION PROFILE OF AN ALZHEIMER'S DISEASE RISK GENE TREM2 VARIANT IN A CO-CULTURE MODEL OF ORGANOIDS AND MICROGLIA.** Kamzina A, Leinenweber KE, Aldabergenova A, Huentelman M. Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

112. **DE-RISKING CLINICAL TRIAL DESIGN VIA MODEL-INFORMED DRUG DEVELOPMENT WITH THE CRITICAL PATH FOR ALZHEIMER'S DISEASE CONSORTIUM**. Karten Y, Jacobsen C, Priest E, Stephenson D, on behalf of the members of the CPAD consortium and CPAD Tau PET Harmonization and Surrogacy Working Groups. Critical Path Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

113. **INVESTIGATING PUBLIC HEALTH IMPACTS OF CARDIOMETABOLIC DISEASES ON INCIDENT DEMENTIA IN THE MEDICARE POPULATION ACROSS THE UNITED STATES**. Karway GK, Krzyzanowski B, Killion JA, Faust I, Laurido-Soto O, Sabbagh M, Racette B. Barrow Neurological Institute; Washington University; University of Witwatersrand, Johannesburg, South Africa; Arizona Alzheimer's Consortium.

114. **NEUROFIBRILLARY TANGLES PREDICT DEMENTIA IN PATIENTS WITH CAROTID STENOSIS.** Khakwani KZR, Zahra S, Butt HI, Acosta D, French S, Vitali F, Arias JC, Hillis M, Howell C, Bolakale-Rufai IK, Courtney K, Bedrick EJ, Beach TG, Serrano G, Weinkauf CC. University of Arizona; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

115. **CROSS-SECTIONAL ASSOCIATIONS BETWEEN PHYSICAL ACTIVITY AND CSF BIOMARKERS OF ALZHEIMER'S DISEASE: THE MAYO CLINIC STUDY OF AGING.** Krell-Roesch J, Syrjanen JA, Kremers WK, Algeciras-Schimnich A, Knopman DS, Jack CR, Petersen RC, Racette SB, Woll A, Vassilaki M, Geda YE. Karlsruhe Institute of Technology, Karlsruhe, Germany; Mayo Clinic, Rochester; Arizona State University; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

116. **STUDY DESIGN OF THE EVALUATION OF SELF-MEDIATED ALTERNATIVES FOR RISK TESTING EDUCATION AND RETURN OF RESULTS (E-SMARTER): A RANDOMIZED TRIAL FROM THE ALZHEIMER'S PREVENTION INITIATIVE (API) PROGRAM.** Langlois C, Bradbury A, Wood BM, Harkins K, Erickson C, Largent E, Egleston B, Reiman EM, Grill J, Roberts JS, Karlawish J, Langbaum JB. Banner Alzheimer's Institute; University of Pennsylvania; University of California, Irvine; University of Michigan; Arizona Alzheimer's Consortium.

117. **ROBUST PCA WITH TRUNCATED WEIGHTED NUCLEAR NORM AND ADAPTIVE HISTOGRAM EQUALIZATION: A NOVEL METHOD FOR LOW-QUALITY RETINAL IMAGE ENHANCEMENT FOR NEURODEGENERATIVE STUDIES.** Likassa HT, Chen K, Wang Y, Zhu W, Sun D, Dumitrascu O, Chen D. Arizona State University; University of Pretoria; Mayo Clinic, Arizona; Indiana University School of Medicine.

118. **NEUROPATHOLOGICAL CORRELATES OF DEMENTIA IN CASES WITH BRAAK NEUROFIBRILLARY STAGE IV.** Lorenzini I, Tremblay C, Aslam S, Beh ST, Walker JE, Intorcia AJ, Arce RA, Borja CI, Cline MP, Qiji SH, Mariner M, Krupp A, McHattie R, Wermager Z, Shull A, Beach TG, Serrano GE. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

119. **LESS SLEEP DURING THE WAKE CYCLE AFTER REPEATED CLOSED HEAD INJURY.** Louangprasert K, McQueen KA, Griffiths DR, Lifshitz J. University of Arizona, College of Medicine-Phoenix; University of Arizona; Phoenix VA Health Care System; Arizona Alzheimer's Consortium.

120. **INTERACTIONS OF VEGF 1154A AND 2578C WITH APOE E4 ON AMYLOID LOAD IN COGNITIVELY UNIMPAIRED OLDER ADULTS.** Malek-Ahmadi M, Piras I, Wang Q, Chen K, Devadas V, Luo J, Su Y. Banner Alzheimer's Institute; Translational Genomics Research Institute; Arizona State University; Arizona Alzheimer's Consortium.

121. **EFFECTS OF PEROXYNITRITE ON VASCULAR SMOOTH MUSCLE CELL BKCA CHANNELS.** Martin PE, Pires PW. University of Arizona; Arizona Alzheimer's Consortium.

122. **TECHNOLOGY PREFERENCES OF INDIVIDUALS WITH MILD COGNITIVE IMPAIRMENT AND FAMILY MEMBERS LIVING IN RURAL COMMUNITIES: A MIXED-METHODS STUDY**. McCarthy MJ, Cerino ES, McCoy MC, Martinez M, Seaton TJ, Goldtooth AD, Livingston RA, Dopson R. Northern Arizona University; Arizona Alzheimer's Consortium.

123. **ENGAGING RURAL SENIOR CENTERS TO SUPPORT COGNITIVE HEALTH: LESSONS FROM THE NORTHERN ARIZONA MEMORY STUDY.** McCoy MC, Cerino ES, McCarthy MJ, Martinez M, Lucero L, Seaton TJ, Goldtooth AD, Livingston RA. Northern Arizona University; Joe C. Montoya Community & Senior Center; Arizona Alzheimer's Consortium.

124. **APOEε4 GENOTYPE ALTERS MYELIN INTEGRITY IN FRONTAL CORTEX WHITE MATTER DURING THE PROGRESSION OF ALZHEIMER'S DISEASE.** Moreno-Rodriguez M, Perez SE, Mufson EJ. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

125. **COLLABORATING TO IDENTIFY AND REDUCE HIGH-RISK MEDICATION USE IN GERIATRICS.** Moyer D, Johnson K, Greiwe L, Patterson T. HonorHealth.

126. **EXPLORING WHITE MATTER MICROSTRUCTURAL ALTERATIONS IN MILD COGNITIVE IMPAIRMENT: A MULTIMODAL DIFFUSION MRI INVESTIGATION UTILIZING DIFFUSION KURTOSIS AND FREE WATER IMAGING.** Nelson MR, Keeling E, Stokes AM, Bergamino M. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.

127. **EXPLORING NEUROGENOMIC DISORDERS THROUGH ORGANOID GENERATION.** Nicholson L, Mosqueda Crespo M, Kamzina A, Taguinod F, Beres S, Piras IS, Huentelman MJ. Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

128. **EXAMINING HEALTH SCIENCES STUDENT ATTITUDES AND KNOWLEDGE OF THE PRIMARY PROGRESSIVE APHASIA (PPA) SYNDROME: A PILOT SURVEY STUDY.** Nickels K, Abraham E, Kielar A. University of Arizona; Arizona Alzheimer's Consortium.

129. **CORRELATION OF AUTONOMIC DYSFUNCTION WITH LEWY BODY PATHOLOGY.** Noe KA, Surdyn M, Adler CH, Mehta SH, Lorenzini I, Walker JE, Theng Beh S, Arce RA, Qiji SH, Intorcia AJ, Borja CI, Cline MP, Krupp AN, McHattie RD, Wermager ZR, Shull A, Mariner MR, Aslam S, Tremblay C, Beach TG, Serrano GE. Banner Sun Health Research Institute; Mayo Clinic College of Medicine.

130. **FRONTAL CORTEX SPLICING PROTEIN U1A AND TAU PATHOGENESIS IN DOWN SYNDROME WITH AND WITHOUT ALZHEIMER'S TYPE DEMENTIA.** Perez SE, Miguel JC, Mufson EJ. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

131. **IDENTIFICATION OF CANDIDATE RNA BLOOD BIOMARKERS IN ALZHEIMER'S DISEASE BY PSEUDOTIME ANALYSIS.** Piras IS, Song S, Naymik M, Ecca F, Huentelman MJ. Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

132. **CELLULAR AND MOLECULAR PHENOTYPES OF DEMENTIA WITH LEWY BODIES VERSUS PARKINSON'S DISEASE WITH DEMENTIA.** Preller K, Antone J, Alsop E, Gittings L, Song S, Beach T, Serrano GE, Pirrotte P, Piras IS, Van Keuren-Jensen K, Sattler R. Barrow Neurological Institute; Translational Genomics Research Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

133. **OPTIMIZING COMPOSITE PET MEASUREMENTS FOR TRACKING LONGITUDINAL TAU ACCUMULATION.** Protas HD, Ghisays V, Luo J, Sohankar J, Lee W, Devadas V, Chen K, Reiman EM, Su Y. Banner Alzheimer's Institute; Arizona Alzheimer's Consortium; University of Arizona; Translational Genomics Research Institute; Arizona State University.

134. **APOE4 EXACERBATES ASTROCYTIC MITOCHONDRIAL DYSFUNCTION-INDUCED NEUROINFLAMMATION AND NEURODEGENERATION**. Qi G, Mi Y, Yin F. University of Arizona; Arizona Alzheimer's Consortium.

135. **LOW FOOD SECURITY IS RELATED WITH MORE MEMORY COMPLAINTS IN A CLINIC-BASED SAMPLE OF LATINO ADULTS**. Saenz J, Tanner L. Arizona State University; Arizona Alzheimer's Consortium.

136. **VALIDATING A BRIEF PERFORMANCE-BASED MEASURE OF COGNITION AND DAILY FUNCTIONING IN OLDER ADULTS**. Schaefer SY, Reed AM, Duff K. Arizona State University; Oregon Health & Science University; Arizona Alzheimer's Consortium.

137. **COMORBIDITIES IN EARLY-ONSET SPORADIC VERSUS PRESENILIN-1 MUTATION-ASSOCIATED ALZHEIMER'S DISEASE DEMENTIA: EVIDENCE FOR DEPENDENCY ON ALZHEIMER'S DISEASE NEUROPATHOLOGICAL CHANGES**. Serrano GE, Sepulveda-Falla D, Villegas Lanau CA, White III C, Acosta-Uribe J, Mejía-Cupajita B, Villalba-Moreno ND, Lu P, Glatzel M, Kofler JK, Ghetti B, Frosch MP, Lopera Restrepo F, Kosik KS, Beach TG. Banner Sun Health Research Institute; University Medical Center Hamburg-Eppendorf; University of Antioquia, Medellin, Colombia; University of Texas Southwestern Medical Center; University of California, Santa Barbara; University of Pittsburgh; Indiana University School of Medicine, Massachusetts General Hospital and Harvard Medical School.

138. **CONTRIBUTION OF ENDOTHELIN SIGNALING TO AD-RELATED CEREBROVASCULAR DYSFUNCTION**. Silva JF, Pires P. University of Arizona; Arizona Alzheimer's Consortium.

139. **CAUSAL RELATIONSHIP BETWEEN SLEEP DURATION AND ALZHEIMER'S DISEASE: INSIGHTS FROM MENDELIAN RANDOMIZATION AND LATENT CAUSAL VARIABLE ANALYSIS**. Song S, Huentelman MJ, Piras IS. Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

140. **ABSENCE OF FMRI REPETITION SUPPRESSION FOLLOWING PERSPECTIVE SHIFTS MAY CONTRIBUTE TO AGE-RELATED SPATIAL MEMORY DEFICITS**. Srokova S, Barnes CA, Ekstrom AD. University of Arizona; Arizona Alzheimer's Consortium.

141. **INJURY-INDUCED AUTOANTIBODIES AS BIOMARKERS FOR ALZHEIMER'S DISEASE.** Stabenfeldt SE, Willingham C, Flores Prieto D, Diehnelt C. Arizona State University; Robust Diagnostics, LLC; Arizona Alzheimer's Consortium.

142. **THE TOPOLOGICAL LANDSCAPE OF PROTEINS ASSOCIATED WITH NEURODEGENERATIVE DISEASE.** Sugiyama M, Kosik KS, Panagiotou E. University of Tennessee at Chattanooga; University of California, Santa Barbara; Arizona State University; Arizona Alzheimer's Consortium.

143. **CAN TREATMENT OF INSOMNIA REDUCE PRECLINICAL BIOMARKERS OF ALZHEIMER'S DISEASE?** Taylor DJ, Huskey A, Emert SE, Nagy SM, Leete J, Kim K, Lopez N, Olson E, Grilli M, Kilgore S. University of Arizona.

144. **BRAIN HEALTH LOTERÍA.** Teposte M, Pazzi M, Martínez L, Nava-Cabrales A, Hernandez M, Diaz C. Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

145. **VALIDATING THE EFFICACY OF A NOVEL POTENT DYRK1A INHIBITOR (DYR533) IN THE TS65DN MOUSE MODEL OF DOWN SYNDROME.** Turk J, Winslow W, Tallino S, Judd J, Bartholomew SK, Mistry F, Hulme C, Dunckley T, Velazquez R. Arizona State University; University of Arizona; Arizona Alzheimer's Consortium.

146. **COMBINING SPEAK OUT!® THERAPY PROGRAM WITH THE COMPUTER ASSISTED REHABILITATION ENVIRONMENT (CAREN) TO IMPROVE SPEECH INTELLIGIBILITY AND GAIT IN PATIENT'S WITH PARKINSON'S DISEASE: A CASE STUDY.** Wash EW, Lamb MA, Manriquez, A, Delap CM. Midwestern University.

147. **PROGRANULIN LEVELS AND LYSOSOMAL FUNCTION ALTER PRO-INFLAMMATORY CYTOKINE PRODUCTION BY MICROGLIA.** Yang AZ, Lin J, Harrison AM, Uppalapati CK, Maqsood S, Biparva P, Leyva KJ, Hull EE. Midwestern University; Arizona Alzheimer's Consortium.

148. **ASYMPTOMATIC EXTRACRANIAL CAROTID ATHEROSCLEROSIS IS ASSOCIATED WITH POORER COGNITIVE FUNCTION AND REDUCTIONS IN WHITE MATTER VOLUME AND PERFUSION.** Zahra S, French SR, Arias JC, Khakwani KZR, Escareno CE, Heitkamp EN, Wiskoski HE, Vazquez F, Ally M, Pugazhendhi A, Culwell GC, Vitali F, Bedrick EJ, Trouard TP, Alexander GE, Weinkauf CC. University of Arizona; Arizona Alzheimer's Consortium.

**149. ADVANCING NUTRIENT DELIVERY IN STRETCHABLE MICROFLUIDIC DEVICES FOR NOVEL ALZHEIMER'S IN-VITRO ANALYSIS.** Bradbeer M, Graudejus O, Rowan C, Wong RP, Wood L, Holberton A. BMSEED; Georgia Tech; Arizona State University.

# Arizona Alzheimer's Consortium
# 25th Annual Scientific Conference

## Oral Research Presentation

## Abstracts

## ORAL RESEARCH PRESENTATION

**RECENT ADVANCES AND CLINICAL IMPLEMENTATION OF BLOOD BIOMARKERS.** Ashton NJ. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

The implementation of blood tests for Alzheimer's disease (AD) would be greatly facilitated by access to easily scalable, cost-effective, and accurate tests. The research community has demonstrated the utility of several biomarkers, such as phosphorylated tau protein (p-tau217), neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP). However, comprehensive data on the clinical relevance of these biomarkers, particularly in primary and secondary healthcare settings, is limited. Expanding research to validate these biomarkers on widely accessible clinical platforms could revolutionize early diagnosis and monitoring of AD, improving patient outcomes and enabling more efficient use of healthcare resources.

This presentation will summarize the latest data on the clinical implementation and significance of blood biomarkers for Alzheimer's disease. It will delve into the nuances of measuring biomarkers such as phosphorylated tau protein (p-tau217), highlighting the differences in various measurement techniques. Additionally, looking towards the future, the presentation will explore advancements in remote blood collection methods, which could enhance accessibility and convenience for patients. Furthermore, it will discuss novel and innovative approaches for discovering biomarkers that are relevant to non-Alzheimer's pathologies and tracking clinical progression, broadening the scope of biomarker utility in neurodegenerative disease research and patient care.

## ORAL RESEARCH PRESENTATION

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

Background: Reactive astrocytes have been implicated in the pathogenesis of C9orf72-FTD/ALS, the most common genetic form of this neurodegenerative disease spectrum. The astrocyte-secreted factor SPARCL1 - a key synaptogenic protein - has been shown to be pivotal to synapse maintenance and strength, yet no studies have carefully addressed whether SPARCL1 dysregulation may contribute to neurodegeneration. Interestingly, decreased SPARCL1 expression in CSF correlates with cognitive impairment in AD (Seddighi et al. JAD 2018, 61 401-414). Our study therefore aimed to ascertain whether similar SPARCL1 perturbations occur in C9orf72-FTD/ALS and how SPARCL1 dysfunction contributes to cortical neurodegeneration.

Methods: iPSCs from C9orf72-FTD/ALS patients (n = 3) and matched controls (n = 3) were differentiated into cortical astrocytes and subjected to bulk RNA-Seq and proteomics analyses. Postmortem frontal cortex tissues from C9orf72-FTD/ALS patients (n = 6) and non-neurological controls (n = 10) were analyzed using snRNA-Seq, with a focus on synaptic maintenance pathways.

Results: We observed a significant reduction of SPARCL1 protein in C9orf72-FTD/ALS patient-derived cortical astrocytes compared to controls ($\log2FC \approx -1.11$; $p = 0.009$). In the frontal cortex of C9orf72-FTD/ALS patients, astrocytic SPARCL1 mRNA levels were similarly diminished ($\log2FC \approx -0.33$; $p < 0.0001$). Furthermore, mRNA levels of several synaptic adhesion molecules, including neurexin and neuroligin family members, were notably decreased in excitatory neurons ($p < 0.0001$).

Conclusions: These data indicate that astrocytic SPARCL1 dysregulation is strongly associated with cortical synaptic dysfunction and neurodegeneration in C9orf72-FTD/ALS. Our ongoing experiments aim to characterize whether SPARCL1 loss directly impinges on synaptic maintenance, with a mechanistic focus on its presumed stabilization of neurexin/neuroligin interactions.

## ORAL RESEARCH PRESENTATION

**ALZHEIMER'S DISEASE-ASSOCIATED CD83(+) MICROGLIA ARE LINKED WITH INCREASED IMMUNOGLOBULIN G4 AND HUMAN CYTOMEGALOVIRUS IN THE GUT, VAGAL NERVE, AND BRAIN.** Readhead BP, Mastroeni DF, Wang Q, Sierra MA, de Ávila C, Jimoh TO, Haure-Mirande J, Atanasoff KE, Nolz J, Suazo C, Barton NJ, Orszulak AR, Chigas SM, Tran K, Mirza A, Ryon K, Proszynski J, Najjar D, Dudley JT, Liu STH, Gandy S, Ehrlich ME, Alsop E, Antone J, Reiman R, Funk C, Best RL, Jhatro M, Kamath K, Shon J, Kowalik TF, Bennett DA, Liang WS, Serrano GE, Beach TG, Van Keuren-Jensen K, Mason CE, Chan Y, Lim ET, Tortorella D, Reiman EM. ASU-Banner Neurodegenerative Disease Research Center, Arizona State University; Weill Cornell Medicine; Icahn School of Medicine at Mount Sinai; University of Massachusetts Chan Medical School; Translational Genomics Research Institute; Institute for Systems Biology; Serimmune, Inc; Rush University Medical Center; Banner Sun Health Research Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Genetic and other studies implicate microglia, the major immune cell type in the brain, in the development and potential treatment of Alzheimer's disease (AD). While there may also be microbial contributions to AD, findings have been inconclusive, and a single pathogen has not been confirmed. In a recent single nucleus RNA sequencing study (Wang, Nat. Commun, 2024) we reported findings from a cohort of 101 subjects (AD n=66, Aged control n=35) who were clinically and neuropathologically well characterized and donated brain and body tissues very soon after they died. In that study we observed a CD83(+) microglial subtype in the superior frontal gyrus of 47% of brain donors with Alzheimer's disease versus 25% of unaffected controls and which was associated with increased Immunoglobulin G4 (IgG4) in the transverse colon (TC). This finding was consistent with a potential microbial interaction between components of the gut microbiome and the presence of CD83(+) microglia.

Methods: Our current study applied a combination of multiomic, multi-tissue and systems biology approaches to investigate this apparent cross-tissue association. This included extensive immunohistochemical studies, IgG4 repertoire profiling, and brain organoid infection experiments. The availability of high-quality tissue from CNS (e.g. brain and CSF) as well as peripheral anatomical sites (e.g. transverse colon, serum) from the same subjects was critical for illuminating these interactions.

Results: Here we report that the presence of CD83(+) microglial in the superior frontal gyrus is significantly associated with elevated immunoglobulin IgG4 and human cytomegalovirus (HCMV) in the transverse colon, increased anti-HCMV IgG4 abundance in the cerebrospinal fluid, and the presence of both HCMV and IgG4 in the superior frontal gyrus and vagal nerve. Examination of AD brain tissue sections from an independent cohort of AD subjects (ROSMAP) confirmed the significant association between HCMV and CD83(+) microglia. HCMV infection of cerebral organoids accelerates production of AD pathophysiological features Aβ42 and pTau-212, while also inducing neuronal death. Further, HCMV infection of immortalized C20 microglia induces expression of CD83, suggesting CD83(+) microglia observed in-situ may be directly infected.

Conclusions: Our results indicate a complex, cross-tissue interaction between HCMV and the host adaptive immune response associated with CD83(+) microglia in persons with AD. Histochemical studies are consistent with an active HCMV infection, suggesting an opportunity for the evaluation of antiviral therapy in older adults with blood-based biomarker evidence of both AD and chronic HCMV infection.

## ORAL RESEARCH PRESENTATION

**ASSOCIATION OF SLEEP BEHAVIORS WITH CEREBRAL WHITE MATTER HYPERINTENSITY VOLUME IN HEALTHY MIDDLE-AGED TO OLDER ADULTS.** Ally M, Aslan DH, Sayre MK, Bharadwaj PK, Maltagliati S, Lai MHC, Wilcox RR, Klimentidis YC, Raichlen DA, Alexander GE. University of Arizona; University of Southern California; Arizona Alzheimer's Consortium.

Background: As dementia prevalence is expected to grow rapidly in the coming decades, recent efforts have focused on understanding how different lifestyle factors influence brain aging. Poor sleep quality has been associated with cognitive decline and increased risk for age-related neurodegenerative disease, however the mechanisms for this are not fully understood. White matter hyperintensity volume (WMHV) measured on magnetic resonance imaging (MRI) reflects a cerebrovascular health factor that has been associated with Alzheimer's disease and vascular dementia and has also been often observed in healthy aging. We investigated the relation between self-reported sleep behaviors and WMHV to evaluate the role of sleep quality in brain aging.

Methods: Middle-aged to older adults (n=10,444) from the UK Biobank were screened to exclude reported major medical (including sleep disorders), neurological, and psychiatric disorders. T1 and T2 FLAIR MRI brain scans measured total WMHV. History of self-reported sleep behaviors were evaluated: (1) hours of sleep/night, (2) daytime napping, (3) sleeplessness, (4) snoring, and (5) daytime dozing. Multiple regression tested associations between each sleep behavior and log-transformed WMHV, while controlling for total intracranial volume, age, sex, ethnicity, education, Townsend Deprivation Index, imaging location, days between visits, depressed mood, and alcohol use (Model 1). Follow-up analyses (Model 2) adjusted for hypertension, diabetes, smoking status, moderate-to-vigorous physical activity, body mass index, and apolipoprotein E (APOE) ε4 status.

Results: The mean (SD) age of the sample was 62.84 (7.53) years, 5,608 were female (53.7%), 10,240 (98.0%) were White, 5,381 (51.5%) had at least a college education, and 2,855 (27.3%) were APOE ε4 carriers. In Model 1, sleep behaviors of increased napping (b=0.069, 95% CI[0.035, 0.103], p<.001), sleeplessness (b=0.041, 95% CI[0.005, 0.078], p=.026), and snoring (b=0.068, 95% CI[0.034, 0.103], p<.001) were associated with greater WMHV, but hours of sleep/night (p=.102) and daytime dozing (p=.369) were not. However, in Model 2 only napping was significantly associated with greater WMHV (b=0.046, CI[0.012, 0.080], p=.007).

Conclusions: In a large cohort of healthy middle-aged to older adults, daytime napping was specifically associated with increased cerebral WMHV. Napping may represent a marker of brain aging, linking sleep quality to white matter pathology, reflecting a potential pathway relating poor sleep to dementia risk. Further research is needed to evaluate causality and clinical outcomes.

## ORAL RESEARCH PRESENTATION

**DEVELOPMENT AND TESTING OF HIGHLY SCALABLE APPROACHES FOR DISCLOSING ALZHEIMER'S GENETIC AND BIOMARKER TEST RESULTS.** Langbaum JB. Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

There is a need to develop and test highly scalable approaches for disclosing Alzheimer's disease (AD) genetic and biomarker test results to research participants and patients. First, the availability of amyloid modifying therapies is dramatically increasing the need for disclosure of AD related genetic and biomarker test results. Second, the 21st Century Cures Act requires the immediate return of most medical test results, including AD biomarkers. Third, there is a shortage of genetic counselors and dementia specialists. One important solution is developing and deploying scalable methods to responsibly communicate gene and biomarker test results. One very promising and proven method is e-health technologies.

This presentation will summarize progress to date in the development and testing of scalable e-health approaches for returning AD genetic and biomarker test results and discuss future directions. It will provide an overview of the APOE genetic counseling and disclosure process used in the Alzheimer's Prevention Initiative (API) Generation Program trial (NCT02565511) and describe the data collected assessing the changes in measures of knowledge, psychological, and emotional wellbeing following disclosure in cognitively unimpaired adults ages 60-75. It will share information about the ancillary CONNECT 4 APOE study (NCT02978729), which randomized persons screening for the Generation Study 1 to receive their results either by telephone or videoconference with a genetic counselor. Lastly, it will discuss the recently launched API eSMARTER trial (NCT06459583) that is evaluating disclosure of APOE and plasma ptau217 by an eHealth platform versus videoconference telehealth disclosure with healthcare providers.

## ORAL RESEARCH PRESENTATION

**APOE, ABCA7, AND RASGEF1C ARE ASSOCIATED WITH EARLIER ONSET OF AMYLOID DEPOSITION FROM OVER 4000 HARMONIZED POSITRON EMISSION TOMOGRAPHY IMAGES.** Castellano T, Wang TC, Wu Y, Archer D, Janve V, Durant A, Regelson A, Cody K, Harrison T, Engelman C, Jagust W, Albert M, Johnson S, Resnick S, Sperling R, Bilgel M, Saykin A, Vardarajan B, Mayeux R, Alzheimer's Disease Neuroimaging Initiative, Betthauser T, Bennett DA, Schneider J, De Jager P, Menon V, Toson D, Mormino E, Dumitrescu L, Hohman T, Koran M. Vanderbilt University Medical Center; Stanford University; University of California, Berkeley; University of Wisconsin; Johns Hopkins University School of Medicine; University of Wisconsin School of Medicine; National Institute on Aging, National Institutes of Health; Massachusetts General Hospital; Brigham and Women's Hospital; Indiana University; Columbia University Medical Center; The New York Presbyterian Hospital; Rush University Medical Center; Columbia University Irving Medical Center; University of California San Francisco; Mayo Clinic Arizona.

Background: Genetics play a significant role in Alzheimer's Disease, but the genetics of the timing of when someone converts to amyloid positivity (the estimated amyloid positivity onset age (EAOA)) remains underexplored. Novel algorithms have shown that the rate of amyloid accumulation is uniform across large cohorts of research participants. Using this uniform rate of accumulation, we can then extrapolate when someone converted to amyloid positivity decades before their PET scans were acquired. We will use these algorithms to calculate EAOA from amyloid PET and then use EAOA in genetics studies to validate APOE associations and explore what genes beyond APOE effect the timing of amyloid onset. As the focus of my K76 aims, this work will be expanded to evaluate the genetics of EAOA in over 18,000+ Aβ PET from the Alzheimer's Disease Sequencing Project--Phenotype Harmonization Consortium.

Methods: Amyloid PET from 4,216 participants were harmonized and the SILA algorithm was utilized to calculate an individual's EAOA. EAOA was then used as an outcome variable in genome wide survival analyses. Gene and pathway analyses, tissue-specific gene expression, and genetic correlations with complex traits were also explored.

Results: APOE ε4 homozygotes converted to amyloid positivity five years earlier than ε3 homozygotes and ~1.5 years earlier than ε3ε4 heterozygotes. rs4147929, an expression quantitative trait loci (eQTL) for the AD-risk gene ABCA7 on chromosome 19 associated with earlier EAOA, with minor allele homozygotes converting to amyloid positivity four years before major allele homozygotes. The minor allele of ABCA7 was associated with increased expression of ABCA7, and increased expression of ABCA7 was associated with increased amyloid pathology in the brain in an independent autopsy dataset. Additionally, the risk-gene RASGEF1C was associated with an earlier EAOA.

Conclusions: Known AD-risk loci APOE, ABCA7, and RASGEF1C were associated with an earlier age of amyloid onset, with supporting evidence from tissue-specific gene expression analyses, offering insights into pathways targetable for intervention at the earliest stages of disease development.

## ORAL RESEARCH PRESENTATION

**DYR533: A NOVEL DYRK1A INHIBITOR AND ITS THERAPEUTIC POTENTIAL IN ALZHEIMER'S DISEASE AND RELATED TAUOPATHIES.** Bartholomew S, Winslow W, Shaw Y, Rokey S, Foley C, Hulme C, Dunckley T, Velazquez R. Arizona State University; University of Arizona; Arizona Alzheimer's Consortium.

Background: The need for pharmaceutical interventions to slow or stop the progression of Alzheimer's Disease (AD) is dire as cases are increasing at an alarming rate. One therapeutic target of interest is dual-specificity tyrosine phosphorylation-regulated kinase 1a (Dyrk1a). Dyrk1a is a ubiquitously expressed protein kinase that directly phosphorylates tau, the Amyloid Precursor Protein (APP) and has been shown to be upregulated in the AD brain. Notably, it is triplicated in Down Syndrome (DS). We find that Dyrk1a protein levels from human post-mortem frontal cortical tissue of control (Braak Stage ≤ III), AD moderate (Braak stage IV) and AD severe (Braak stage VI) negatively correlate with last Mini Mental State Exam, and positively correlate with Braak Stage, Neuritic plaque density, and pro-inflammatory cytokine Tumor Necrosis Factor (TNF)-α. Given the relationship between Dyrk1a and hallmark AD pathogenesis, our goal was to determine the efficacy of a novel and potent Dyrk1a inhibitor termed DYR533 in reducing the AD-like pathology modeled in PS19 and 3xTg-AD mice.

Methods: Prior to the accumulation of tau, four-month-old PS19 mice and their non-transgenic (NonTg) control littermates were given daily intraperitoneal injections of either 1.0, 2.5, or 5.0 mg/kg of DYR533 or a Vehicle control for four months. At 7 months, all subjects were put through a battery of behavioral tasks to assess motor function and spatial learning and memory, then euthanized at 8 months when brain tissue and blood plasma were collected. In a second study, prior to the presence of amyloid-β (Aβ) and tau pathogenesis, 7.5-month-old female 3xTg-AD and NonTg mice were dosed with DYR533 (using the same doses as PS19 experiment) until 10 months of age followed by brain tissue and blood collection.

Results: We found that PS19 mice dosed with DYR533 showed improved performance in the Rotarod, a test of motor function, and the Morris Water Maze, a test of spatial learning and memory. Neuropathological assessment of PS19 brain tissue revealed that DYR533 significantly reduced Dyrk1a protein levels in both hippocampal (Hp) and cortical (Ctx) tissue, in addition to reducing phosphorylated tau (pTau) at the pathologically relevant epitopes Serine 396 (S396) and Threonine 181 (T181) and reduced pro-inflammatory cytokine TNF-α in both the brain and blood plasma. 3xTg-AD mice given DYR533 consistently showed significant reductions in Hp and Ctx Dyrk1a protein levels, pTau S396 and T181, TNF-α, and soluble cortical Aβ42.

Conclusions: Collectively, this work strongly supports the efficacy of the novel DYR533 in mitigating hallmark pathogenesis and improving neuroinflammation seen in the AD brain, which has broader implications for its use as a therapeutic in other tauopathies and Down Syndrome.

## ORAL RESEARCH PRESENTATION

**ASYMPTOMATIC EXTRACRANIAL CAROTID ATHEROSCLEROSIS IS ASSOCIATED WITH POORER COGNITIVE FUNCTION AND REDUCTIONS IN WHITE MATTER VOLUME AND PERFUSION.** Zahra S, French SR, Arias JC, Khakwani KZR, Escareno CE, Heitkamp EN, Wiskoski HE, Vazquez F, Ally M, Pugazhendhi A, Culwell GC, Vitali F, Bedrick EJ, Trouard TP, Alexander GE, Weinkauf CC. University of Arizona; Arizona Alzheimer's Consortium.

Background: There is increasing evidence that carotid stenosis is associated with cognitive impairment and dementia. But little is known about the associated changes in the brain. Although the brain has robust collateral blood flow and perfusion regulation, a potential mechanism for how carotid stenosis could result in cognitive decline is through chronic brain hypoperfusion. In the brain, white matter more than gray matter is susceptible to the vascular damage induced by chronic hypoperfusion. We investigated whether asymptomatic extracranial atherosclerotic disease (aECAD) is associated with cognitive impairment and whether that impairment is linked to white matter changes including hypoperfusion and volume loss.

Methods: A total of 150 study participants with a diagnosis of aECAD and/or ≥2 cardiovascular risk factors between the ages of 50-85 years were recruited from vascular clinics in Tucson, AZ. Participants underwent MRI scans to evaluate carotid stenosis percentage, brain volumes, and cerebral perfusion. Brain volumes were adjusted for total intracranial volume (TIV) prior to analysis. Pseudo-continuous Arterial Spin Labelling (pcASL) was used to measure perfusion signals. ASL images were analyzed using BASIL toolbox available in FMRIB Software Library (FSL). Each participant also underwent a neurocognitive testing battery. Spearman-rank correlation was used to assess the association between the continuous variables. Cognitive status among perfusion groups was compared using Wilcoxon rank sum test. Linear regression was used to control for potential confounders.

Results: Wechsler Adult Intelligence Scale (WAIS) Coding, WAIS Symbol Search, and the Stroop Color-Word test, which assess processing speed and executive function, were negatively correlated with carotid stenosis ($p<0.01$). Degree of carotid stenosis was inversely associated with white matter perfusion ($r= -0.32$, $p<0.01$) and white matter volume ($r=-0.28$, $p<0.01$). The decrease in perfusion was consistent even after adjusting for age, sex, cardiovascular risk factors and white matter lesion volumes. ($\beta$ coefficient= -0.27, $p= 0.03$). The group with low-perfusion had lower WAIS Coding scores compared to the high-perfusion group ($p=0.05$), while other cognitive tests (WAIS Symbol Search, Stroop Color-Word test) did not differ significantly.

Conclusions: Asymptomatic extracranial atherosclerotic disease is associated with poorer cognition, white matter hypoperfusion and white matter volume reduction. Still more, in a small subset of participants (n=15), we found that surgical treatment significantly increased perfusion compared to baseline. Understanding mechanisms of cognitive dysfunction associated with aECAD will build impetus for more targeted treatments in this population that currently is not clinically evaluated or treated for cognitive outcomes.

## ORAL RESEARCH PRESENTATION

**DEVELOPMENT OF A COMPOSITE SCORE TO PREDICT LEWY BODY PATHOLOGY BURDEN.** Choudhury P, Chen K, Zhang N, Tremblay C, Ho AH, Belden CM, Adler CH, Shill H, Mehta S, Driver-Dunckley E, Shprecher DR, Serrano GE, Beach TG, Reiman EM, Atri A. Banner Sun Health Research Institute; Arizona State University; University of Arizona; Banner Alzheimer's Institute; Mayo Clinic Arizona; Barrow Neurological Institute; Brigham and Women's Hospital; Harvard Medical School; Arizona Alzheimer's Consortium.

Background: Lewy body (LB) diseases can present with overlapping prodromal, cognitive, motor, autonomic or neuropsychiatric symptoms. Intuitively, greater symptom severity should correlate with greater pathological burden, but this has not been consistently shown. LB pathology does not translate to clinical expression in Incidental LB disease. While several composite scores/toolkits utilize overlapping schemes for diagnosis, a composite data-derived score to predict LB pathologic burden is lacking. We aimed to utilize an autopsy-confirmed cohort, and validated, brief, and standardized clinical, functional, pathologic assessments, and machine learning (ML)/quantitative modeling techniques to identify clusters and importance rankings among assessments/measures to predict LB pathologic severity and density.

Methods: A total of 234 subjects with neuropathological finding of LB at autopsy in the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) who were classified as Cognitively Unimpaired or Mild Cognitive Impairment after their first study clinical evaluation were included. Of these, 145 subjects had complete scores for 32 of 46 measures (clinical, cognitive, behavioral and functional) that were utilized as predictors of LB pathology. Olfactory function was assessed using the University of Pennsylvania Smell Identification Test (UPSIT). LB severity was assess by the Unified Staging System for Lewy Body Disorders (USSLB). Several ML algorithms and quantitative prediction models were explored and compared: artificial neural network (ANN), partial least square regression (PLSR), support vector regression (SVR), relevance vector regression (RVR) and ensemble forest regression (EFR) with leave-one-out (LOO) scheme. Game-theory based Shapley methods assessed the impact, including rankings, consistency and magnitude, of model predictors.

Results: RVR predicted aggregate LB density with large effect size ($R2 = 0.691$, $p < 0.00001$). ANN predicted USSLB severity stage with large effect size ($R2 = 0.74$, $p < 2.5e\text{-}43$). All other ML algorithms/models provided substantial prediction. Across all models, UPSIT was the most influential predictor (>65%), followed by Controlled Oral Word Association Test (COWAT) and age.

Conclusions: These preliminary and exploratory results support the utilization of ML techniques/models to assess LB pathologic burden with key measures collected in relatively small samples. UPSIT was consistently ranked highest impactful among clinical and functional measures/predictors. Integrated together in ML/data-derived composites, UPSIT, COWAT and other clinical characteristics may be of antemortem utility to predict USSLB stages.

## ORAL RESEARCH PRESENTATION

**DEVELOPMENT AND DEPLOYMENT OF A MOBILE NEUROIMAGING LABORATORY FOR THE STUDY OF AGE-RELATED CHANGES IN RESIDENTS OF RURAL ARIZONA ZIP CODES.** Price C, Dock K, Chambers D, Metz D, Ahearn ME, Sharma S, Karaniuk K, Determan R, Perry G, Davis C, Johnson M, Beres S, De Both M, Venkatachalam H, Naymik M, Taguinod F, Bonfitto A, Huentelman M. Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: A challenge facing all disciplines of human research is the engagement, recruitment, study, and retention of typically understudied societal groups. This is critical so that any public health recommendations, diagnostic tests, or therapeutics have the highest chance of being generalizable across the population. One such understudied group are those individuals who reside in rural zip codes. They are critical to enroll in research studies because they are known to exhibit different risk factors and environmental exposures when compared to their non-rural peers. Our MindCrowd study excels in the study of underserved groups; with approximately 80% of our cohort representing membership in one or more of the recognized understudied categories. To recruit rural participants, we developed a mobile research laboratory (mLab) and launched a sub-study of MindCrowd that we call Mobile Minds.

Methods: The mLab consists of a custom-built 28-foot horse trailer that includes two rooms; a wet laboratory and a neuroimaging suite. It supports multiple phenotyping approaches including blood collection and ultra-low-field MRI (0.06 Tesla; 1.5mm voxel size). The Mobile Minds protocol includes measurement of blood pressure, grip strength, body composition, scent detection, processing speed, verbal memory, and T1/T2 volumetric MRI. A 0.5 c.c. capillary bed blood sample is also collected and processed for DNA and plasma biomarkers.

Results: Since November of 2023, the mLab has enrolled and studied over 600 participants from over 10 different Arizona cities; 50% of which reside in rural zip codes. We observe predicted trends in all phenotypic measures, including age- and sex-related effects on grip strength, body composition, scent detection, cognition, brain region volumes, and plasm biomarkers.

Conclusions: We demonstrated that a mobile laboratory approach for the study of rural Arizona residents is well received and capable of phenotypically assessing multiple domains associated with typical aging and age-related cognitive disease. This approach will continue to be employed and 1-year longitudinal assessments of the cohort will begin in November. We propose that greater use of this and other innovative approaches for engagement, recruitment, and retention of understudied societal groups will play an important role in the future of human research.

# Arizona Alzheimer's Consortium
# 25th Annual Scientific Conference

## Student Poster Presentation

## Abstracts

## STUDENT POSTER # 1

**CORTICOSTERONE DISRUPTS SPATIAL WORKING MEMORY DURING RETENTION TESTING WHEN HIGHLY TAXED, WHICH POSITIVELY CORRELATES WITH DEPRESSIVE-LIKE BEHAVIOR IN MIDDLE-AGED, OVARIECTOMIZED FEMALE RATS.** Acuña AM, Peay DN, Whittaker K, Donnay ME, Conrad CD. Arizona State University; Arizona Alzheimer's Consortium.

Background: Major Depressive Disorder (MDD) affects 8.4 % of the U.S. population and is twice as common in women than men. Moreover, women are particularly vulnerable to developing MDD during hormonal fluctuations, especially during the menopausal transition. Stress is associated with the development of MDD, overlapping in brain circuitry and function. To investigate mechanisms of MDD, chronic stress in rodents is commonly employed, but often show mixed reports as to whether females express more depressive-like behavior compared to males, which questions the face validity of chronic stress in preclinical models. Many of these reports use young adult females or aged females, but few study middle-age. Moreover, estrogens can have some protective qualities that could obscure the results. The current study tested the hypothesis that chronic exposure to the rodent stress hormone, corticosterone (CORT) would result in heightened depressive-like behavior, comorbid expression of anxiety-like behavior, and impaired spatial working memory in middle-aged, ovariectomized (OVX) female rats.

Methods: OVX Female rats (12 months) were exposed to CORT (400 µg/ml or vehicle, VEH) in drinking water for approximately two months. At 28 days of the CORT treatment, rats began behavioral tests that included depressive-like assessments (Sucrose Preference (SP), Forced Swim Test (FST), and Social Interactions), anxiety-like assessments (Novelty Suppressed Feeding (NSF), Elevated Plus Maze (EPM), Marble Bury) and cognitive assessments (eight arm Radial Arm Water Maze (RAWM), Visible Platform (VP).

Results: Compared to VEH-treated rats, CORT significantly intensified depressive-like behaviors: decreased SP, enhanced immobility on the FST, and decreased sociability. CORT enhanced anxiety-like behavior on a marble bury task by reducing time investigating. No effects were observed on NSF or the EPM. CORT did not alter the ability to learn a spatial working memory version of the RAWM; however, when the rats acquired the rules of the task, CORT disrupted performance when rats had most items to remember. As CORT-treated rats performed well during VP, this suggested that CORT disrupted spatial working memory, as opposed to motivation or motor skills. Finally, a composite depressive-like behavior score positively correlated with poor spatial working memory to show that as depressive-like symptoms increased, cognitive performance worsened.

Conclusions: OVX middle-aged females expressed depressive-like behaviors, anxiety-like behaviors and cognitive dysfunction when exposed to stress levels of CORT for an extended duration. Moreover, depressive-like behavior and poor spatial working memory were highly correlated. This study is the first to show that CORT-treated, middle-aged OVX females expressed a variety of symptoms that are commonly observed with depression, including helplessness, anhedonia, anxiety, and cognitive fog, by using a protocol that allowed for the inclusion of multiple behavioral assessments.

## STUDENT POSTER # 2

**ASSOCIATION OF SLEEP BEHAVIORS WITH CEREBRAL WHITE MATTER HYPERINTENSITY VOLUME IN HEALTHY MIDDLE-AGED TO OLDER ADULTS.** Ally M, Aslan DH, Sayre MK, Bharadwaj PK, Maltagliati S, Lai MHC, Wilcox RR, Klimentidis YC, Raichlen DA, Alexander GE. University of Arizona; University of Southern California; Arizona Alzheimer's Consortium.

Background: As dementia prevalence is expected to grow rapidly in the coming decades, recent efforts have focused on understanding how different lifestyle factors influence brain aging. Poor sleep quality has been associated with cognitive decline and increased risk for age-related neurodegenerative disease, however the mechanisms for this are not fully understood. White matter hyperintensity volume (WMHV) measured on magnetic resonance imaging (MRI) reflects a cerebrovascular health factor that has been associated with Alzheimer's disease and vascular dementia and has also been often observed in healthy aging. We investigated the relation between self-reported sleep behaviors and WMHV to evaluate the role of sleep quality in brain aging.

Methods: Middle-aged to older adults (n=10,444) from the UK Biobank were screened to exclude reported major medical (including sleep disorders), neurological, and psychiatric disorders. T1 and T2 FLAIR MRI brain scans measured total WMHV. History of self-reported sleep behaviors were evaluated: (1) hours of sleep/night, (2) daytime napping, (3) sleeplessness, (4) snoring, and (5) daytime dozing. Multiple regression tested associations between each sleep behavior and log-transformed WMHV, while controlling for total intracranial volume, age, sex, ethnicity, education, Townsend Deprivation Index, imaging location, days between visits, depressed mood, and alcohol use (Model 1). Follow-up analyses (Model 2) adjusted for hypertension, diabetes, smoking status, moderate-to-vigorous physical activity, body mass index, and apolipoprotein E (APOE) ε4 status.

Results: The mean (SD) age of the sample was 62.84 (7.53) years, 5,608 were female (53.7%), 10,240 (98.0%) were White, 5,381 (51.5%) had at least a college education, and 2,855 (27.3%) were APOE ε4 carriers. In Model 1, sleep behaviors of increased napping (b=0.069, 95% CI[0.035, 0.103], p<.001), sleeplessness (b=0.041, 95% CI[0.005, 0.078], p=.026), and snoring (b=0.068, 95% CI[0.034, 0.103], p<.001) were associated with greater WMHV, but hours of sleep/night (p=.102) and daytime dozing (p=.369) were not. However, in Model 2 only napping was significantly associated with greater WMHV (b=0.046, CI[0.012, 0.080], p=.007).

Conclusions: In a large cohort of healthy middle-aged to older adults, daytime napping was specifically associated with increased cerebral WMHV. Napping may represent a marker of brain aging, linking sleep quality to white matter pathology, reflecting a potential pathway relating poor sleep to dementia risk. Further research is needed to evaluate causality and clinical outcomes.

## STUDENT POSTER # 3

**SUPPORTIVE ENVIRONMENT FOR AGING: EXPLORING THE IMPACT OF MULTISENSORY ENVIRONMENTS ON SLEEP, MOOD, AND STRESS IN OLDER ADULTS WITH BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA.** Alrahyani M, Yeom D, Guest A, Lesselyong J, Fani M, Sharp N. Arizona State University; Qassim University; ViewPoint Senior Care; Arizona Alzheimer's Consortium.

Background: The ambient indoor environment feature is one of the most influential factors in assisted long-term care facilities that has significant impact on patients' psychological and physiological responses. The multi-sensory environment has gained wide attention as a non-pharmacological intervention that may contribute to delaying the worsening severity of neurocognitive disorders from the mildest to the most severe stages in older adults with dementia and other cognitive impairments. Studies have reported the impact of the multi-sensory environment on depression, agitation and functional performance of the older adults diagnosed with dementia. However, the typical MSE in these studies (Snoezelen room) demands special requirements (e.g., Trained therapist and MSE facilitator) and expensive equipment. Furthermore, these studies did not investigate the impact of MSE on the sleep quality of BPSD patients. Thus, the purpose of this study is to examine the effectiveness of a novel MSE approach on BPSD patients' sleep quality and other physiological/psychological responses via a series of human experiments.

Methods: A field study was conducted on 12 older adults (age > 53 years old) diagnosed with BPSD in the partner memory care facility. Our study introduced cost-effective and passive MSEs, Multi-Sensory Stimulating Environment (MSSE) and Multi-Sensory Relaxing Environment (MSRE), using a combination of sensory stimuli, including visual stimuli, aroma, and sound. Over six consecutive weeks, participants underwent a baseline week in their conventional environment, followed by three weeks of 6-day MSE interventions, each separated by a week washout period. Interventions included exposure to MSSE in Week 2 during morning, exposure to MSRE in Week 4 during evening, and a combination of both (morning and evening) in Week 6. The impact of each intervention on the participant's sleep and heart rate (HR, stress) were assessed via a non-invasive wearable device (Fitbit). Additionally, the Cornell Scale for Depression in Dementia (CSDD) and the Cohen-Mansfield Agitation Inventory (CMAI) were used to assess depression and agitation. The questionnaires were completed by primary caregivers to provide comprehensive insights into participants' responses.

Results: Our findings indicate significant reduction in depressive symptoms in participants after exposure to all three interventional conditions with most notable improvements during the combined exposure. Interventions descriptively showed longer sleep duration compared to the baseline. Furthermore, heart rate was observed to be lower during the exposure to the interventions suggesting calming effects.

Conclusions: The results highlight the potential of cost-effective and passive MSEs to enhance the quality of life for older adults with BPSD, offering practical guidance for more accessible MSE implementations in diverse care settings.

## STUDENT POSTER # 4

**LOCATING YOUR NEXT DESTINATION ACROSS PROGRESSIVE MEMORY LOADS: DO SURGICAL MENOPAUSE VARIANTS IMPACT SPATIAL PRECISION?** Anyigbo K, Doyle RT, Oevermann MW, Kelley-Wolfe K, Badhwar N, Roorkeewal G, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.

Background: In the United States, approximately one-third of women will experience uterine removal, or hysterectomy, by age 60, often before the natural onset of menopause. In roughly half of the hysterectomy cases, the ovaries are retained to prevent premature surgical menopause. Surgical procedures for menopause can also include removal of both ovaries, or bilateral oophorectomy. Hysterectomy alone, and bilateral oophorectomy, each increase the risk for dementia in women. In many research studies, women are grouped together based on ovarian status without accounting for the presence or absence of the uterus, thereby obscuring whether outcomes relate to hysterectomy status. Our laboratory developed a rat model of hysterectomy to further expand cognitive assessments of surgical menopause variants used in women, and to decipher the individual impact of uterine removal. With this model, we have shown unique detrimental impacts on spatial working memory performance resulting from hysterectomy surgery alone on a water radial-arm maze task with a systematically elevating working memory load. We have also previously demonstrated ovarian hormone modulation of spatial precision while solving this task; yet, comparative effects of clinically-given menopause surgeries have not been systematically tested but could yield insight into the breadth and depth of spatial impacts. Thus, the current study implemented our previously-developed precision analysis to evaluate the comparative spatial acuity of varied clinically-utilized surgical menopause models, including hysterectomy.

Methods: Reproductively inexperienced Fischer-CDF female rats were randomly assigned to surgical treatment groups of Sham, Hysterectomy, and Ovariectomy (Ovx). After recovery from surgery, rats were trained on an eight-arm water-escape radial-arm maze task in which animals needed to locate a hidden platform for escape. This maze measures spatial working memory as load increases. Every error choice was quantified relative to the correct arm via determining how many arms away the choice was from the nearest platformed arm.

Results: Preliminary analyses indicate that for spatial precision, the impact of menopause varied with working memory load demand, with the greatest changes in spatial precision occurring at the highest load. Further analyses are ongoing and will be presented at the poster session.

Conclusions: These results will inform further interpretations of spatial ability after hysterectomy and other menopause variants via characterizing spatially localized choices and providing fine-tuned context of spatial precision on a multiple-choice maze task.

## STUDENT POSTER # 5

**AN ENHANCED COGNITIVE COMPOSITE TEST SCORE WITH THE SENSITIVITY TO PREDICT AND MONITOR PROGRESSION IN THE WORLD'S LARGEST AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE KINDRED.** Badhwar N, Ghisays V, Malek-Ahmadi MH, Li S, Su Y, Reiman EM. Arizona State University; Banner Alzheimer's Institute; Mayo Clinic; Translational Genomics Research Institute; University of Arizona; Arizona Alzheimer's Consortium.

Background: For preclinical Alzheimer's disease trials, it is essential to identify a set of sensitive tests that offer prognostic value. We used longitudinal cognitive data derived from the Colombian Alzheimer's Prevention Initiative Autosomal Dominant Alzheimer's Disease (API ADAD) trial to calculate mean-to-standard deviation ratios (MSDR), regression tree analysis, and principal component analysis (PCA) to identify cognitive tests that are sensitive to preclinical AD decline.

Methods: 5-year mean-change and SD's were used to calculate MSDR values in 166 PSEN1 mutation carriers who participated in the trial. The following tests were used: 11 subsets of the RBANS, Ravens Progress Matrices, and the Free Cued and Selective Reminding Test (FCSRT) immediate and delayed recall. Regression tree models, random forest models, and PCA models were used to determine which tests best predicted Clinical Dementia Rating Sum of Boxes (CDR-SOB) score.

Results: FCSRT immediate (0.83) and FCSRT delay (0.78) yielded the highest MSDR scores. Regression tree analysis indicated RBANS coding, FCSRT delay, and RBANS story recall as the best predictors (MSDR1.76, 1.48, 1.91, respectively). Random Forest (RF) yielded RBANS Coding, RBANS Story Recall, and FCSRT delay (r2= 0.586). PCA indicated RBANS coding and FCSRT immediate (r = 0.73, 0.51, respectively).

Conclusions: We conclude that FCSRT and RBANS coding and story recall may be the most sensitive tests for tracking cognitive decline in this population. These tests may be used in future clinical trials to better inform a person's subsequent cognitive course and accurately estimate treatment effects.

## STUDENT POSTER # 6

**DYR533: A NOVEL DYRK1A INHIBITOR AND ITS THERAPEUTIC POTENTIAL IN ALZHEIMER'S DISEASE AND RELATED TAUOPATHIES.** Bartholomew S, Winslow W, Shaw Y, Rokey S, Foley C, Hulme C, Dunckley T, Velazquez R. Arizona State University; University of Arizona; Arizona Alzheimer's Consortium.

Background: The need for pharmaceutical interventions to slow or stop the progression of Alzheimer's Disease (AD) is dire as cases are increasing at an alarming rate. One therapeutic target of interest is dual-specificity tyrosine phosphorylation-regulated kinase 1a (Dyrk1a). Dyrk1a is a ubiquitously expressed protein kinase that directly phosphorylates tau, the Amyloid Precursor Protein (APP) and has been shown to be upregulated in the AD brain. Notably, it is triplicated in Down Syndrome (DS). We find that Dyrk1a protein levels from human post-mortem frontal cortical tissue of control (Braak Stage ≤ III), AD moderate (Braak stage IV) and AD severe (Braak stage VI) negatively correlate with last Mini Mental State Exam, and positively correlate with Braak Stage, Neuritic plaque density, and pro-inflammatory cytokine Tumor Necrosis Factor (TNF)-α. Given the relationship between Dyrk1a and hallmark AD pathogenesis, our goal was to determine the efficacy of a novel and potent Dyrk1a inhibitor termed DYR533 in reducing the AD-like pathology modeled in PS19 and 3xTg-AD mice.

Methods: Prior to the accumulation of tau, four-month-old PS19 mice and their non-transgenic (NonTg) control littermates were given daily intraperitoneal injections of either 1.0, 2.5, or 5.0 mg/kg of DYR533 or a Vehicle control for four months. At 7 months, all subjects were put through a battery of behavioral tasks to assess motor function and spatial learning and memory, then euthanized at 8 months when brain tissue and blood plasma were collected. In a second study, prior to the presence of amyloid-β (Aβ) and tau pathogenesis, 7.5-month-old female 3xTg-AD and NonTg mice were dosed with DYR533 (using the same doses as PS19 experiment) until 10 months of age followed by brain tissue and blood collection.

Results: We found that PS19 mice dosed with DYR533 showed improved performance in the Rotarod, a test of motor function, and the Morris Water Maze, a test of spatial learning and memory. Neuropathological assessment of PS19 brain tissue revealed that DYR533 significantly reduced Dyrk1a protein levels in both hippocampal (Hp) and cortical (Ctx) tissue, in addition to reducing phosphorylated tau (pTau) at the pathologically relevant epitopes Serine 396 (S396) and Threonine 181 (T181) and reduced pro-inflammatory cytokine TNF-α in both the brain and blood plasma. 3xTg-AD mice given DYR533 consistently showed significant reductions in Hp and Ctx Dyrk1a protein levels, pTau S396 and T181, TNF-α, and soluble cortical Aβ42.

Conclusions: Collectively, this work strongly supports the efficacy of the novel DYR533 in mitigating hallmark pathogenesis and improving neuroinflammation seen in the AD brain, which has broader implications for its use as a therapeutic in other tauopathies and Down Syndrome.

## STUDENT POSTER # 7

**EFFICACY OF MUSIC INTERVENTIONS FOR PERSONS LIVING WITH DEMENTIA ON ACTIVITIES OF DAILY LIVING**. Bentien K, Beck A, Turner T. Midwestern University.

Background: With the growing evidence and diagnosis of dementia the concern for a person's ability to live independently is an important factor in managing their plan of care as their disease progresses. Identifying areas that can be preserved is a supportive measure to enable independence. The objective of this systematic review was to determine the effects of therapeutic music interventions on activities of daily living (ADL) for persons living with dementia?" Research articles included in the review gathered data from residents of skilled nursing facilities who had the diagnosis of mild, moderate, or severe dementia. The Barthel Index (BI) and the Functional Independence Measure (FIM) were used to measure the effects of music intervention with OT intervention on ADL independence for persons living with dementia.

Methods: The database PubMed was searched in accordance with EBSCOhost using the search criteria of "music interventions" "activities of daily living" and either "dementia" or "Alzheimer's disease". Inclusion criteria comprised of randomized controlled trials with participants diagnosed with dementia, above the age of 65, and with music intervention, including music stimulation, singing/auditory stimulation, lyric reading, or clapping. Exclusion criteria comprised of participants diagnosed with decreased visual or auditory acuity.

Results: Four articles were included with a combined 380 participants. The randomized controlled trials, evidenced by meta-analysis, identified overall pooled effect size 0.061 (95% confidence interval).. Although the meta-analysis favored occupational therapy with music intervention the results were not statistically significant.

Conclusions: Identifying non-pharmaceutical interventions to maintain ADL independence for individuals living with dementia increases quality of life. This meta-analysis did not find that music interventions improved ADL function, indicating that future research on how occupational therapy practitioners can maintain or improve ADL function is needed.

## STUDENT POSTER # 8

**MEASURING CEREBRAL WHITE MATTER CHANGES IN ALZHEIMER'S DISEASE USING THE AMYLOID PET TRACER FLORBETAPIR.** Bhargava V, Luo J, Devadas V, Malek-Ahmadi M, Chen K, Reiman EM, Su Y. University of Arizona, College of Medicine-Phoenix; Banner Alzheimer's Institute; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Recent studies have demonstrated the use of amyloid PET tracers in studying White Matter Hyperintensities (WMHs), areas of increased white matter signal intensity in T2-weighted MRIs, in Alzheimer's disease (Moscoso et al. 2022, European Journal of Nuclear Medicine). Here, we further compare the amyloid PET tracer, Florbetapir, uptake in white matter to T2-weighted FLAIR measured WMHs and their relationship to AD-specific Amyloid, Tau, Neurodegeneration, and Inflammation ("ATNI") biomarkers.

Methods: Baseline and 2.40±1.0 year follow-up Florbetapir data from n=775 mild AD dementia, mild cognitive impairment (MCI), and cognitively unimpaired (CU) participants from Alzheimer's Disease Neuroimaging Initiative (ADNI) were used to characterize and compare the association between cross-sectional Florbetapir uptake in white matter to T2-weighted FLAIR WMHs. Participants were further divided into amyloid positive vs amyloid negative individuals using a centiloid threshold of >20 and cognitive decline status (positive or negative) using Clinical Dementia Rating threshold of greater than 0. Florbetapir uptake was calculated using Standardized Uptake Value Ratios (WM SUVRs) and cerebellar cortex as the reference region. Florbetapir WM SUVRs and total T2-weighted FLAIR WMHs volumes were then compared to ATNI imaging (mean cortical amyloid Florbetapir PET and Flortaucipir tau PET) and blood-based biomarkers (phosphorylated-tau 181 (ptau-181), Neurofilament Light Chain Protein (NfL), Glial Fibrillary Acidic Protein (GFAP)) using partial correlations (co-varying for age and education).

Results: WMH volumes were associated with lower Florbetapir WM SUVRs (R=-0.29, p=7.50E-14). With increasing AD disease severity, baseline values of Florbetapir WM SUVRs decreased while WMH volumes increased. Florbetapir WM SUVRs were significantly associated with PET and blood-based biomarkers of amyloid (Florbetapir WM SUVR/mean cortical Florbetapir PET: R=-0.17, p=1.60E-05; Florbetapir WM SUVR/ptau181: R=-0.22, p=1.40E-08), Flortaucipir measured tau deposition in the Entorhinal Cortex (R=-0.18, p <0.001), and neurodegeneration biomarkers (Florbetapir WM SUVR/plasma NfL R-0.14, p=3.00E-04). WMH volumes were significantly associated with amyloid and neurodegeneration biomarkers but not with tau-PET deposition in the Entorhinal Cortex (WMH Volume/mean cortical Florbetapir PET (R=0.28, p=3.70E-13); WMH Volume/ptau181 (R=0.19, p=2.60E-06); WMH Volume/plasma NfL (R=0.28, p=1.90E-12) ; WMH Volume/Entorhinal Cortex PET tau deposition (R=0.04, p=0.47). In a sub-sample where relevant data was available, both WMH volumes and Florbetapir WM SUVRs were not associated with plasma GFAP (WMH Volumes/plasma GFAP: R=0.26, p=0.15; Florbetapir WM SUVRs/plasma GFA: R=0.00, p=0.98).

Conclusions: This study further supports the use of amyloid Florbetapir PET tracer in studying white matter changes in AD pathology.

## STUDENT POSTER # 9

**GENOTYPIC EFFECT ON MICROBIOME COMPOSITION IN A DROSOPHILA MELANOGASTER MODEL OF PARKINSON'S DISEASE.** Bonnette PE, Olson SC, Chagolla SM, Pearman K, Zhu H, Ludington WB, Call GB. Midwestern University; Carnegie Institution for Science; Johns Hopkins University; Arizona Alzheimer's Consortium.

Background: While motor and neurological symptoms are the primary hallmark of Parkinson's disease (PD), PD patients regularly suffer from non-motor symptoms, including gastrointestinal issues such as gut dysbiosis and constipation. These gut manifestations of a neurodegenerative disease have supported the hypothesis of a gut-brain axis (GBA). The Call lab has been investigating the potential GBA involvement in PD using a Drosophila melanogaster model. Previous experiments in our lab have shown that park25 flies have a large increase in bacterial colonization when compared to control flies, which is the basis for these experiments.

Methods: To further investigate the colonization pattern of PD model flies, we inoculated axenic park25 and control Drosophila embryos with a set concentration of four different bacterial stocks: Lactobacillus brevis, Lactiplantibacillus plantarum, Acetobacter pomorum, and Acetobacter tropicalis. The embryos were either mono-associated with one bacterial strain or given a combination inoculation of all four. Following genotypic selection of the pupae, the food was reinoculated with the same strains and adult flies were collected at ages 6-7 days to be homogenized and plated. In some experiments, the gut was dissected and separated into distinct sections (head and foregut, cardia and midgut, Malpighian tubules, crop, hindgut, and carcass) before homogenization. The subsequent bacterial colonies were counted and the colony forming units (CFUs)/fly were calculated. To investigate if the loss of Parkin in the crop was responsible for colonization differences, crop-specific expression of a parkin-RNAi construct was performed. In addition to our homozygous park25 flies, trans-heterozygous park25 models were used to confirm our results. To visualize the bacterial load in the gut, control and park25 pupae were inoculated with a fluorescent L. plantarum strain, aged out to 6-7 days, dissected and imaged on a confocal microscope.

Results: It was determined that most of the increased bacterial colonization was occurring in the crop, with all other sections showing no significant difference between park25 and control flies. While not significant, the midgut also appeared to be increased in the level of colonization. Similar results were obtained by the fluorescent bacterial imaging, which showed a consistent increased fluorescent intensity in the crop of park25 flies while the midgut sometimes had an increased fluorescent signal. RNAi knockdown of park had no increase in bacterial load compared to control flies.

Conclusions: Dissection of the gut revealed that the crop had higher CFUs when compared to control flies and fluorescent imaging appeared to support this phenotype. This suggested that Parkin loss in the crop may lead to an autonomous increase in bacterial colonization. Interestingly, RNAi knockdown of park in the crop revealed that loss of Parkin is not responsible for this phenomenon. Therefore, we are pursuing a feeding assay along with a constipation assay to determine if a gut motility issue may be contributing to the increased colonization seen in our PD model flies. This could have direct implications in human PD patients that experience a very high frequency of both constipation and gut dysbiosis.

**STUDENT POSTER # 10**

**ENHANCING ALZHEIMER'S DIAGNOSIS: LEVERAGING ANATOMICAL LANDMARKS IN GRAPH CONVOLUTIONAL NEURAL NETWORKS ON HIPPOCAMPAL TETRAHEDRAL MESHES.** Chen Y, Su Y, Farazi M, Yang Z, Fan Y, George J, Wang Y. Arizona State University; Banner Alzheimer's Institute; Amazon AGI.

Background: MRI captures brain structural information and has been widely used in AD diagnosis. Hippocampus has been proven to be directly related to human memory and associated with AD progression and dementia. While machine learning and deep learning methods have been widely used on voxel images and surface meshes, volumetric meshes are less studied. Recently, a novel method, TetCNN, was proposed for tetrahedral mesh data analysis based on volumetric Laplace Beltrami operator (volumetric LBO). In this study, we developed a novel approach to AD diagnosis based on TetCNN, enhanced by anatomical landmarks generated via Gaussian process.

Methods: Our proposed network architecture consists of a 5-layer graph neural network, where graph convolution was approximated by Chebyshev polynomial and graph Laplacian was replaced by volumetric LBO. We further enhanced the model by integrating pre-computed anatomical landmarks generated by the Gaussian process. We proposed a landmark fusion (LF) layer that incorporates anatomical landmarks through an attention mechanism, resulting in an improved statistical power.

Results: We downloaded 523 AD, 381 MCI, and 328 CN samples from the ADNI database. The collected MRI images were processed by Freesurfer for surface reconstruction and hippocampus segmentation. The tetrahedral mesh was generated by TetGen. We performed group-wise classification between all possible pairs of the diagnosis groups. As a result, our model outperformed baseline methods, including TetCNN, pointNet and pointNet++, yielding accuracies of 0.908±0.014 in AD vs CN, 0.798±0.023 in AD vs MCI and 0.695±0.028 in MCI vs CN, respectively. Ablation study also showed the significance of transformer encoder module in our model.

Conclusions: In this study, we introduced a novel geometric deep learning-based algorithm for Alzheimer's disease diagnosis using brain hippocampal structure. Our model was constructed upon the TetCNN backbone, a recently proposed geometric deep learning method optimized for tetrahedral mesh feature extraction. By incorporating anatomical landmarks, our result demonstrated an improved performance compared to baseline models.

## STUDENT POSTER # 11

**PLASMA CYCLEGAN: INTEGRATING BLOOD-BASED BIOMARKERS FOR CROSS-MODALITY TRANSLATION FROM MRI TO PET.** Chen Y, Su Y, Fu Y, Chen K, Weidman D, Caselli RJ, Reiman EM, Wang Y. Arizona State University; Banner Alzheimer's Institute, Phoenix; Zhejiang University; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Cross-modality translation between MRI and PET presents significant challenges due to the distinct mechanisms underlying those modalities. Currently, the leading method for this translation is CycleGAN. Previous studies have proved a strong correlation between blood-based biomarkers (BBBMs) and brain amyloid status measured by PET. However, the impact of BBBMs on PET image synthesis has not yet been thoroughly evaluated. In this study, we propose Plasma CycleGAN, a generative model based on CycleGAN to synthesize PET images from MRI, while also incorporating BBBMs and other clinical covariates. We show that Plasma CycleGAN outperforms the state-of-the-art CycleGAN for MRI-to-PET translation. Our method is the first to integrate BBBMs in a conditional cross modality translation from MRI to PET.

Methods: Our model was built on CycleGAN architecture, while the backbone was improved by integrating BBBMs as additional conditions in the input domain. To be specific, we introduce a masked perturbation in the MRI image, whose voxel-level magnitudes are learnable parameters in the neural network. The dataset we used to evaluate our model is downloaded from the ADNI database. The cohort contains 667 subjects with matching BBBM, T1-weighted MRI images, amyloid PET, and clinical features, including age, sex, weights, etc. The synthesized PET images are compared with the ground truth PET images for performance evaluation using traditional metrics like structural similarity index (SSIM), peak-signal-to-noise ratio (PSNR) and mean square error (MSE). In addition, the Pearson correlation coefficients (PCCs) of the masked SUVR ratios were calculated.

Results: We evaluated the baseline CycleGAN model using MRI input, as well as combined inputs of MRI+BBBM and other clinical features. Our model achieved an SSIM of 0.78±0.13, PSNR of 25.47±2.27 and MSE of 214.23±139.41 in PET image synthesis task using MRI+ Aβ42/40, both yielding the best results among all input combinations.

Conclusions: We introduce Plasma CycleGAN, the first generative model to integrate BBBMs and clinical features in PET image synthesis from MRI images. In PET image synthesis task, our proposed integrated model outperforms the baseline CycleGAN model.

## STUDENT POSTER # 12

**EXAMINING SEX-RELATED COGNITIVE AND NEURAL DIFFERENCES IN JUVENILE AND MIDDLE-AGED MICE IN A PAIRWISE VISUAL DISCRIMINATION TASK.** Christiansen K, Truong V, Bowser S, Lyle T, Bimonte-Nelson H, Verpeut J. Arizona State University; Arizona Alzheimer's Consortium.

Background: Dementia-related disorders are a proliferating concern for the healthcare industry, with 10% of the population being over 65 (Ritchie & Roser, 2024). While many studies have tracked the rate of cognitive decline during the later stages of dementia, there is an absence of research examining the rates of decline during early dementia. Additionally, the lack of female-specific dementia research poses a health disparity for healthcare professionals who rely on research-based therapeutics, with men receiving higher quality medication management and therapies (Sourial et al., 2020). It is critical to understand the symptoms of early-onset dementia in male and female individuals to allow for better individualized healthcare and an increased understanding of how cognition wanes across the lifespan. We hypothesized that juvenile female mice would exhibit equal cognitive performance compared to males, but would undergo more drastic cognitive decline into middle-age.

Methods: Cognitive changes across the lifespan were examined in both male (n=35) and female (n=31) C57BL/6J juvenile (postnatal day 21) and middle-aged (10 months of age ) mice using a pairwise visual discrimination task. During this task, animals learned to associate the correct image selection with sweetened condensed milk (15%) reward. The acquisition stage tested each animal's learning ability by measuring the percentage of successful image selections over 10 days. The correct shape was switched in the reversal stage to analyze cognitive flexibility for 10-15 days or until reaching criteria (70%). Trial initiation, response, and reward collection latencies were analyzed using the sum of average medians for each mouse. Following testing, brain tissue was analyzed for dendritic complexity and spine density using Golgi-Cox staining.

Results: We found that there are no significant differences in cognitive ability nor cognitive flexibility between sexes amongst the juvenile and aged cohorts, yet aged females are quicker to collect rewards ($p < 0.05$). Among male animals, there are no significant differences in cognitive ability and cognitive flexibility between juvenile and aged groups. However, among females, juvenile animals exhibit better cognitive ability and cognitive flexibility ($p < 0.05$), demonstrated by more correct choices during early relearning. Neurological analysis in layer 2/3 of the somatomotor region found that juvenile animals display an increased number of dendritic intersections further away from the soma regardless of sex ($p < 0.05$).

Conclusions: This current work establishes age-related sex-specific changes in the visual discrimination task, which will be used to quantify changes in neural pathology and brain structure as we continue to analyze multiple brain regions. Our research will ultimately contribute to a more nuanced understanding of sex and aging and their implications for better individualized dementia treatments.

**STUDENT POSTER # 13**

**SEX DIFFERENCES FOR TRAJECTORIES OF PLASMA-NFL AND MRI REGION OF INTEREST CHANGE IN COGNITIVELY UNIMPAIRED LATE-MIDDLE-AGED AND OLDER ADULTS.** Clyde C, Malek-Ahmadi M, Su Y, Ghisays V, Luo J, Devadas V, Chen Y, Lee W, Protas H, Chen K, Zetterberg H, Blennow K, Caselli RJ, Reiman EM. Dine College, Tsaile, AZ; Banner Alzheimer's Institute, Phoenix; Arizona State University; University of Gothenburg; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is a neurodegenerative disease affecting approximately 6.9 million people in the United States. Approximately two-thirds of all AD cases are women who are thought to be at a higher risk for AD compared to men. Neurofilament light (NfL) is an indicator of neurodegeneration and/or neuroaxonal injury and is not specific to one etiology of neurodegeneration. Here we examined sex differences on the trajectory of plasma NfL as well as the trajectory of change for thickness and surface area in regions of interest.

Methods: Dataset total of 151 cognitively unimpaired (CU) participants (42 male and 109 female) from the Arizona APOE Cohort were used for this analysis. Linear mixed models were adjusted for baseline age, years of education, and APOE genotype were used to derive annualized change scores for plasma NfL as well as changes in regions of interest. In the linear mixed models a time (years) by sex interaction was used to estimate the rate of change for each participant. Cohen's d was used to quantify the effect size of annualized change differences between males and females. Hippocampal volume was used as a reference to compare the regions of interest derived from the linear mixed models. for paracentral gyrus thickness, entorhinal cortex surface area, and temporal pole surface area.

Results: Trajectories of hippocampal volume ($p=0.9906$, $d = -0.128$) and plasma NfL ($p=0.2807$, $d = -0.019$) did not differ between males and females. Paracentral gyrus thickness ($p = 0.0099$), entorhinal cortex surface area ($p = 0.019$), and temporal pole surface area ($p = 0.0302$) showed significant sex-based differences with women having higher rates of neurodegeneration in these regions. Effect sizes for the differences in annualized change between females and males were: temporal pole surface area ($d = 0.077$), entorhinal surface area ($d = 0.001$ ), paracentral gyrus thickness ($d = 0.401$).

Conclusions: The trajectory of plasma NfL change does not differ between males and females, however females have faster rates of paracentral gyrus thinning as well as entorhinal cortex and temporal surface area reduction in contrast to men. However, for hippocampal volume males had shown a much faster rate of decline. These findings suggest sex-specific neurodegenerative patterns in cortical areas typically associated with AD. Future studies should give greater consideration to regional differences in neurodegeneration between males and females.

## STUDENT POSTER # 14

**MUSIC DURING MEALTIME IN RESIDENTIAL SETTINGS: CAREGIVER EXPERIENCES AND PERSPECTIVES.** Colussi K, Venkatesh M. A.T. Still University.

Background: The purpose of the study was to explore the experiences of healthcare caregivers regarding playing music during mealtime for people living with dementia in residential settings. People living with dementia usually present with age-related feeding and swallowing difficulties. Additionally, due to their cognitive decline, they may lose their drive to eat and drink; and may get easily distracted resulting in poor oral intake (Watson, 2006). Anxiety and depression could also lead to poor oral intake (Amella et al, 2008). Inadequate oral intake can lead to an increased rate of hospitalizations, falls, cognitive impairment, and dependency on caregivers for activities of daily living (Borders, 2020). Healthcare professionals, such as certified nursing assistants, activity coordinators, and nurses often choose and play music in the dining room during mealtime. Currently, there is a limited understanding of what motivates the staff in the facility to select music and what their experiences are regarding the impact of playing music every day during mealtime.

Methods: Healthcare caregivers in residential settings (skilled nursing facilities, long-term care settings, memory care centers) were sent a survey to complete. The 25-item survey measured experiences regarding music and mealtime behaviors of people living with dementia.

Results: 28 healthcare caregivers completed the survey. Preliminary results indicate that healthcare caregivers experience positive effects of playing music during mealtime including independence in feeding and eating, independence using utensils, decreased need for assistance, increased communication with caregivers and other residents, better mood, and decreased agitation. Residents preferred classical music and music from the 70's.

Conclusions: Caregiver experiences indicate that playing music during mealtime benefits people living with dementia in residential settings.

## STUDENT POSTER # 15

**EFFICIENT DIFFUSION MRI MEASUREMENTS OF TISSUE MICROSTRUCTURE WITH SPHERICAL AND PLANER TENSOR ENCODING.** Comrie CJ, Galons JP, Beach TG, Serrano GE, Hutchinson EB. University of Arizona; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Recently, non-gaussian microstructural MRI methods such as mean apparent propagator (MAP-MRI) have emerged with sensitivity to spatial features on the order of microns and may detect changes in the brain tissue environment like cellularity, morphology, or protein accumulation that are more sensitive and specific than the conventional diffusion tensor imaging (DTI) method. However, implementing these methods into a clinical setting is challenging due to the time, hardware, and image processing needs required by these higher-order models. Alternative diffusion acquisition methods have recently been developed such as q-space trajectory imaging (QTI) that use continuous waveforms and may generate diffusion weighted images (DWIs) that report targeted microstructural information in a model-free manner at a fraction of the time. This study aims to evaluate a range of QTI DWI encodings by comparison to ground truth diffusion microscale-anisotropy and restriction metrics.

Methods: Imaging was performed on a formalin-fixed post-mortem human temporal lobe specimen acquired from Banner Sun Health Institute, and was prepped and suspended in Fluorinert. Images were acquired on a 7T Bruker Biospec MRI scanner using a multi-shell acquisition with 201 DWI volumes over b =0-6,000 s/mm2 at an isotropic resolution of 250 microns, taking ~48 hours. Diffusion pre-processing and MAP-MRI calculations were performed with TORTOISE 3.2.0 to generate PA and RTOP. QTI waveforms were developed using NOW software for STE and PTE, acquired at gradient strengths of G=26-166 mT/m over 6 directions for 24 DWI volumes each at an isotropic resolution of 200 microns, with each scan taking ~20 minutes. QTI DWI volumes were averaged over the 6 directions for both waveforms, and histogram analysis was performed for the whole specimen for PA and RTOP maps and QTI images.

Results: Histogram analysis in PA and RTOP, were used as "ground truth" references and revealed two dominant peaks: lower values for gray matter neurites and higher values for white matter myelinated axon bundle pathways. PA also showed a third intermediate peak for axonal pathways within gray matter regions. Histogram analysis in PTE and STE indicated that as gradient strengths increased, intensity values decreased, with PTE being more influenced by higher gradient strengths than STE. Despite expectations, the gradient strengths and directional averaging in PTE did not fully capture the PA distribution. However, RTOP and STE showed resemblance at the highest gradient strength (166 mT/m), suggesting adequate probing of isotropic restriction.

Conclusions: The STE waveform was successful in probing similar compartments mapped in high-order models, while the PTE waveform needs further development for gradient weightings, timings, and angular sampling to mimic the PA distribution. Future developments and validations are planned for both waveforms, and will also be extended to Alzheimer's Disease specimens.

## STUDENT POSTER # 16

**CNS-ACTIVE DRUGS FOR NEUROPSYCHIATRIC DISORDERS DIFFERENTIALLY MODULATE RISK OF AD DEVELOPMENT.** Cortes-Flores H, Torrandell-Haro G, Diaz Brinton R. University of Arizona; Arizona Alzheimer's Consortium.

Background: Neuropsychiatric disorders including depression, insomnia, epilepsy, schizophrenia and attention-deficit and hyperactivity disorder (ADHD) have been associated with a neurodegenerative process and linked to increased risk for Alzheimer's Disease (AD). Because of shared biological mechanisms of AD and neuropsychiatric disorders, we hypothesized that pharmacologic treatment for neuropsychiatric disorders could impact risk for AD. CNS drugs that are first-line therapies for neuropsychiatric disorders (including antidepressants, sedatives, anticonvulsants, antipsychotics and stimulants) were investigated for impact on AD incidence.

Methods: To address this hypothesis, we conducted a retrospective medical informatics analysis of insurance claims of patients aged 60 years and older, with and without exposure to CNS drugs. To reduce health status and demographic bias, we utilized propensity score matching to adjust for age, gender, Charlson comorbidity index (CCI), and comorbidities. The propensity score matched population was surveyed for AD diagnosis following at least 1 year of exposure to CNS drugs.

Results: Exposure to CNS drugs was associated with a decreased risk for AD (RR [95%CI]: 0.50 [0.47–0.53]; P<.0001), and women (RR [95%CI]: 0.46 [0.42–0.50]; P<.0001) exhibited a slightly greater risk reduction compared to men (RR [95%CI]: 0.55 [0.50–0.61]; P<.0001). Drug stratification indicated that antidepressant, sedative, anticonvulsant, and stimulant treatment were associated with reduced AD risk, while antipsychotics were associated with increased risk for AD. Additional analysis indicated that the combination of two CNS drugs was associated with a greater reduction of AD risk compared to monotherapy for most drugs assessed. Age and sex emerged as modulators of rate of disease conversion, with females older than 70 years receiving the greatest benefit.

Conclusions: Collectively, these results indicate that antidepressants, sedatives, anticonvulsants, and stimulants are beneficial as risk modifiers for AD, while antipsychotics appear to increase the vulnerability of the brain for AD development. Potential use of combination therapy with antipsychotics could mitigate the risk conferred by these drugs. These findings have the potential to contribute to advancing neuropsychiatric treatment that could impact risk of Alzheimer's disease.

**STUDENT POSTER # 17**

**TDP-43 SEVERITY IS NOT ASSOCIATED WITH COGNITIVE DOMAIN DISPERSION IN COGNITIVELY UNIMPAIRED AND MILD COGNITIVE IMPAIRMENT AUTOPSY CASES.**

Crosby S, Malek-Ahmadi M, Perez SE, Mufson EJ. University of Arizona; Banner Alzheimer's Institute; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Previous studies have shown that transactive response DNA protein-43 (TDP-43) severity is associated with decreased cognitive performance, independently of Alzheimer's disease (AD) plaque and tangle pathology. Dispersion, or greater variation in performance between cognitive domains, has been implicated as an early cognitive marker for progression to mild cognitive impairment (MCI) and AD. The aim of this study is to determine whether TDP-43 severity is associated with cognitive domain dispersion as well as performance in several cognitive domains in a well-characterized autopsy cohort.

Methods: 138 cognitively unimpaired (CU; mean age = 86.00±6.01; 56% female) and 91 mild cognitive impairment (MCI; mean age = 88.95±6.61; 67% female) cases from the Rush Religious Orders Study were used. Cognitive data from each subjects last clinic visit were used which included composite z-scores for Episodic Memory, Semantic Memory, Working Memory, Visuospatial, and Perceptual Speed. The intrasubject standard deviation (ISD) of the cognitive composite z-scores was used to quantify cognitive domain dispersion. TDP-43 severity was assessed using a standardized 0-3 scale with higher scores indicating greater severity. Linear regression models were used to assess the association of TDP-43 severity with cognitive domain dispersion and each of the individual cognitive domains while adjusting for age at death, sex, years of education, APOE ε4 carrier status, CERAD neuritic plaque severity, Braak stage, cerebral amyloid angiopathy severity, and clinical diagnosis.

Results: The primary analysis found that TDP-43 severity was not associated with cognitive domain dispersion ($\beta = 0.019$, 95% CI: (-0.015, 0.053), $p = 0.28$). When each of the cognitive domains were analyzed, greater TDP-43 severity was associated with decreased episodic memory performance ($\beta = -0.17$, 95% CI: (-0.26, -0.078), $p = 0.00034$), but was not significantly associated with any other cognitive domains.

Conclusions: TDP-43 shows a different relationship to cognitive ability compared to other AD-related pathologies. Unlike previous studies that demonstrated a relationship between cognitive dispersion and amyloid plaques, TDP-43 was not associated with dispersion. Out of all tested cognitive domains, TDP-43 pathology was greatly associated with episodic memory function. Increased deposition of TDP-43 correlated with decreased episodic memory ability in a stage-dependent manner. Further exploration is needed to determine if TDP-43 attenuation improves episodic memory performance. Understanding TDP-43's role in AD progression may be a key part of improving episodic memory and thus quality of life for AD patients and those with TDP-43-related disorders.

**STUDENT POSTER # 18**

**THE SYNTHESIS OF NEUROMODULATORY MOLECULES BY A GUT MICROBIAL GLUTAMATE DECARBOXYLASE: GABA, TAURINE AND ITS ANALOGS, AND B-ALANINE.**

Dadi P, Pauling CW, Shrivastava A, Shah DD. Arizona State University; Arizona Alzheimer's Consortium.

Background: Dysbiosis in the human gut microbiome has been implicated as a contributing factor to various neurological disorders, although the precise mechanism of disease onset remains unclear. Prior research has linked gut microbes to the production of γ-aminobutyric acid (GABA), a neurotransmitter critical in neurodegenerative diseases such as Alzheimer's (AD) and dementia, where decreased GABA levels are consistently observed. Multiple investigations on the microbiomes of individuals suffering from AD and dementia have consistently shown differences in the abundance of microbes from the genus Bacteroides, which encode the gene for the enzyme glutamate decarboxylase (GAD). We hypothesized that Bacteroides fragilis GAD (BfGAD) plays a role in GABA production and explored its potential involvement in synthesizing other neuromodulatory molecules such as taurine and its derivatives, which have cytoprotective and GABAA receptor agonist properties. Lower taurine levels have been linked to cognitive deficits, while taurine supplementation improves cognitive function in murine models.

Methods: We characterized BfGAD and investigated its ability to decarboxylate L-glutamate to produce GABA. Kinetic parameters of the enzyme were determined using spectrophotometric assays. Additionally, chromatographic techniques were used to analyze the activity towards other non-native substrates.

Results: BfGAD effectively decarboxylated L-glutamate to produce GABA along with other neuromodulatory molecules such as taurine and its analogs, and β-alanine. Engineered BfGAD led to improved taurine production, with a single amino acid modification showing a 2-fold increase.

Conclusions: Our work suggests that the gut microbial glutamate decarboxylase activity can be fine-tuned to modulate the concentrations of neuromodulatory molecules. Specifically, understanding the role of BfGAD and its engineered variants in production of neuromodulatory molecules can be utilized for potential therapeutic interventions.

## STUDENT POSTER # 19

**THE ORAL TRAIL MAKING TEST: NORMATIVE ANALYSIS FOR OLDER ADULTS**. Dessert A, Malek-Ahmadi MH, Blake L, Auman B, Belden C, Atri A, Arce R, Serrano G. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Midwestern University; Arizona Alzheimer's Consortium.

Background: The written Trail Making Test (WTMT) is a well-established two-part measure utilized by neuropsychologists given its sensitivity towards detecting cognitive decline (Mrazik et al., 2010). WTMT-A is a simple visual scanning task whereas WTMT-B adds an executive function component of set shifting. While the WTMT-B is a sensitive measure for identifying cognitive dysfunction as an individual ages, non-cognitive factors also frequently associated with older adults, including reduced visual acuity and motor difficulties, hinder one's ability to complete the task, thus impacting interpretation bearing on diagnosis (Mrazik et al., 2010). To address these limitations, an oral version of the Trail Making Test (OTMT) was developed (Ricker & Axelrod, 1994). Although other researchers have compiled normative data on the OTMT (Abraham et al., 1996; Bastug et al., 2013; Kowalczyk et al., 2001; Mrazik et al., 2010; Wadsworth et al., 2016), these samples have been relatively small with limited representation of older adults. Furthermore, the demands for neuropsychological assessments capable of being delivered in a virtual format rose exponentially following the COVID-19 pandemic; however, neuropsychology has few cognitive assessments capable of being administered in this modality (Carotenuto et al., 2021; Zeghari et al., 2022). Therefore, the present study has developed normative data for the OTMT in an older adult population to encourage clinical utility, particularly for teleneuropsychological assessments.

Methods: Neuropsychological test data was collected from 164 adults over the age of 65 currently enrolled in the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) and Brain and Body Donation Program (BBDP). Exclusion criteria included a phone Montreal Cognitive Assessment (MoCA) score below 18 out of 20 as this would be indicative of cognitive decline and the inability to complete the OTMT. Along with the OTMT, data from the Stroop Color Word test and CLF phonemic fluency test.

Results: Individuals were placed into five-year increment groups by age with calculated OTMT completion time means and standard deviations. Spearman correlational analyses were conducted to examine the relationship between the OTMT and other processing and executive control measures to further establish construct validity. There was a significant negative relationship observed between OTMT-A and Stroop Color ($r(132) = -0.355$, $p < 0.0001$) and Stroop Word ($r(133) = -0.444$, $p < 0.0001$). Significant negative correlations were also observed between OTMT-B and Stroop Color/Word condition ($r(129) = -0.314$, $p = 0.003$) and a CFL phonemic fluency task ($r(169) = -0.273$, $p = 0.0003$).

Conclusions: Results were consistent with previous research demonstrating the OTMT's construct validity with other processing speed and executive functions measures. This supports the use of normative data for measures, such as the OTMT, that help to reduce an artificial increase in processing speed (i.e., motor difficulties) that may not accurately reflect an individual's cognitive functioning. Preliminary data reinforces the use of the OTMT in a virtual format as these data provide normative values for the OTMT that could be expanded upon.

## STUDENT POSTER # 20

**A NOVEL APPROACH FOR DETECTING AGE-RELATED CHANGES IN THE EX-VIVO FEMALE BONNET MACAQUE BRAIN USING MULTI-PARAMETRIC MRI.** Dieckhaus L, McDermott K, Gray DT, Barnes CA, Hutchinson EB. University of Arizona; University of California, Los Angeles; Arizona Alzheimer's Consortium.

Background: While several quantitative maps derived from magnetic resonance imaging (MRI) have shown promise in detecting age-related brain changes, it remains unclear which of these maps provides the most information. We used a novel analysis method to identify aged-related changes across the female bonnet macaque whole brain that can evaluate the predictive power of different combination of MRI maps. Our approach required an organism that has known lifespan-related brain changes with MRI, making non-human primates the ideal candidate. Additionally, ex vivo whole brain imaging allows for collection of a myriad of MRI map types at high resolution, allowing for a more comprehensive comparison.

Methods: Diffusion and relaxometry derived MRI maps were obtained at 200-to-600-micron resolution isotropic in seven female bonnet macaque ex vivo brain specimens ranging in age from 10-34 years. Diffusion-based maps included Fractional Anisotropy, Axial Diffusivity, Radial Diffusivity, and Trace, which measure diffusion of water and assesses white matter tract geometry. Relaxometry-based maps included T2, R2star, Myelin Water Fraction, and Bound Pool Fraction, which measure the biophysical properties of tissue such as myelin and iron content. These maps were warped to a template space for group analysis. We classified adult (14-21 years, n=3) vs. aged (28-34 years, n=4) brains using three MRI datasets: all metrics, diffusion-only, and relaxometry-only. For each voxel in the brain, the accuracy of predicting aged versus adult was calculated.

Results: The all metric dataset, which had a mean of 90% accuracy, which was higher compared to diffusion only and relaxometry only which had means around 60%. We identified regions with the highest density of accurate classification (above 90%) and found that the thalamus and the hippocampus contained 60% and 33%, respectively. Of the 3 datasets , all metrics outperformed diffusion and relaxometry only models significantly in the thalamus (Cohen's D range=3.64,5.14, compared to diffusion-only and relaxometry-only respectively; $p<0.001$) and hippocampus (Cohen's D= 3.4 ,3.76, compared to diffusion-only and relaxometry-only respectively; $p<0.001$). No significant differences were observed between diffusion-only and relaxometry-only datasets.

Conclusions: These results suggest a mixed effect of MRI map types on identifying age-related changes in the brain. Our novel analysis method revealed that combining multi-parametric MRI maps can improve the prediction of age-related changes in the brain more accurately than using a more traditional univariate analysis approach.

**STUDENT POSTER # 21**

**INVESTIGATING THE EFFECTS OF ORALLY ADMINISTERED BACTEROIDES FRAGILIS ON MICE MODELING ALZHEIMER'S DISEASE PATHOLOGIES.** Dikshit S, Conn K, Barroso-Montalvo D, Monarrez DV, Finkle H, Caporaso G, Cope EK. Northern Arizona University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is a progressive, irreversible neurodegenerative condition marked by amyloid-β plaques and neurofibrillary tangles in the brain, leading to cognitive decline, anger, depression, and personality changes (Borsom et al. 2023; Li et al. 2014). The incidence of AD is increasing rapidly with the aging population, expected to triple in the next 30 years ("2020 Alzheimer's Disease Facts and Figures" 2020). There are no effective treatments, necessitating a deeper understanding of disease mechanisms, including the role of microglial activation and gut-brain axis communication. The gut-brain axis involves communication through immune, nervous, metabolic, and endocrine pathways (Martin et al. 2018). Imbalance in gut microbiota can increase intestinal permeability, release proinflammatory cytokines, and promote neuroinflammation (Medzhitov 2007). Recent studies suggest that Bacteroides fragilis (Bf) is enriched in the gut microbiota of AD patients and may trigger microglial activation (Xia et al. 2023). These findings highlight the potential role of gut bacteria in AD pathogenesis.

Bacteroides fragilis (Bf) is a Gram-negative, anaerobic bacterium integral to the human gut microbiome, involved in immune development, pathogen protection, and metabolism (Xia et al. 2023). Its influence extends to systemic health and neurological conditions. Animal studies indicate that manipulating gut microbiota with specific strains like Bf can affect amyloid-β deposition, neuroinflammation, and cognitive function. This study investigates the effect of Bf treatment on the gut microbiome in 3xTg-AD mice. It compares the gut microbiome of Bf-treated 3xTg-AD mice, untreated 3xTg-AD mice, and their wild-type (WT) cohorts.

Methods: Fecal samples were collected from 117 mice (61 Bf-treated, 56 control) every two weeks from 4 to 52 weeks of age. Key timepoints included 8 weeks (baseline), 24 weeks (amyloid-β plaque modeling), and 52 weeks (both plaques and neurofibrillary tangles modeling). DNA from these samples was extracted using MagMAX™ Pathogen RNA/DNA Kit and underwent 16S amplification. Sequencing was performed using MiSeq Reagent Nano Kit, with data analyzed via Qiime2.

Results: 3xTg-AD mice had higher early-life Bf abundance compared to WT mice. WT mice, regardless of treatment, had more native Bacteroides species. WT mice treated with Bf showed decreased Lactobacillus levels compared to other groups. Bf treatment altered the fecal microbiome uniquely for each mouse strain. AD-modeling mice showed decreased Gabra-1 expression and early-life Bf exposure reduced mucin-2 expression, which later recovered.

Conclusions: Bf treatment modulates the gut microbiome in a strain-specific manner, influencing gut microbial community structure and potential AD pathogenesis. Understanding these dynamics can aid in developing new therapeutic strategies for AD.

## STUDENT POSTER # 22

**END-TO-END 3D CYCLEGAN MODEL FOR AMYLOID PET HARMONIZATION.** Dong X, Shah J, Ghisays V, Luo J, Chen Y, Lee W, Li B, Wu T, Reiman EM, Chen K, Wang Y, Su Y. Arizona State University; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Amyloid PET (Positron Emission Tomography) is crucial in detecting amyloid burden within the brain. However, the diversity of amyloid tracers and the scarcity of paired data significantly challenge the collaboration between cross-center studies. In this research, we introduce a novel patch-based 3D end-to-end image transformation model. This model works as a harmonization strategy, transferring the amyloid PET images from one tracer type to another.

Methods: 51 florbetapir (FBP) and 604 PiB images from the Australian Imaging, Biomarkers and Lifestyle Study of Ageing (AIBL) were processed using established pipelines to extract regional standard uptake value ratios (SUVRs), mean cortical SUVRs (mcSUVRs), and SUVR images. 3D Cycle-Consistent Generative Adversarial Networks (CycleGAN) was used to learn the end-to-end 3D image transformation using adversarial training strategies in conjunction with Resnet generators and multilayer discriminators within different tracer domains. Data augmentation techniques were applied to process the FBP images to balance the training samples and patch-based learning was used throughout the experiment. The trained CycleGAN model was then applied to an independent dataset with 46 paired images from www.gaain.org/centiloid-project for performance evaluation. Correlation analyses were conducted voxel-wise and on mcSUVR, comparing the FBP/synthetic PiB to the true PiB data. The Structural Similarity Index Measure (SSIM) and Peak Signal-to-Noise Ratio (PSNR) were also evaluated between the synthetic and real PiB SUVR images.

Results: The synthetic PiB SUVR images were visually more similar to real PiB SUVR images than FBP. Voxel-wise correlation improved from 0.942 between FBP and real PiB to 0.958 between the virtual and real PiB SUVR image ($p < 0.0001$). The agreement of mcSUVR improved from $r = 0.909$ to $r = 0.954$ ($p<0.001$) in the independent test dataset. The SSIM and PSNR between synthetic and real PiB are 0.762 and 25.370 in the independent dataset.

Conclusions: We proposed a novel end-to-end image transformation model for 3D PET image synthesis. The model finds the nonlinear mapping between different tracers and eliminates the requirement for paired training images. The result was confirmed using an independent dataset to demonstrate its effectiveness.

## STUDENT POSTER # 23

**END-TO-END 3D CYCLEGAN MODEL FOR MRI HARMONIZATION.** Dong X, Shah J, Ghisays V, Luo J, Chen Y, Lee W, Li B, Wu T, Reiman EM, Chen K, Wang Y, Su Y. Arizona State University; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is the most prevalent form of age-related dementia, impacting 6.2 million people aged 65 or older, according to CDC data. Many ongoing studies are using neuroimaging techniques to investigate AD. However, technical variabilities related to image acquisition across different centers and studies limit the full power of these studies. In this research, we introduce a novel patch-based 3D end-to-end image transformation model based on neural networks as a harmonization strategy, transferring 1.5 Tesla (T) MRI to 3T MRI images.

Methods: A total of 1131 1.5T and 3T MRI images from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database were processed and used in the experiment. We employed 3D Cycle-Consistent Generative Adversarial Networks (CycleGAN) to learn the end-to-end 3D image transformation using adversarial training strategies, with ResNet generators and multilayer discriminators in fields of different magnetic strengths. Data augmentation techniques were applied to process the MRI images, and patch-based learning was utilized throughout the experiment. The trained CycleGAN model was then applied to 100 unpaired images from the ADNI datasets for performance evaluation. Since there were no paired images in the testing set, the 3D-ResNet10 pretrained on 23 medical datasets from MedicalNet was used to extract features. Model performance was assessed based on the Frechet Inception Distance (FID) score.

Results: The synthetic 3T MRI images were visually more similar to real 3T MRI images than to 1.5T MRI images. The FID score dropped from 5.003 between virtual 3T and 1.5T MRI images to 3.617 between real and virtual 3T MRI images.

Conclusions: We proposed a novel end-to-end image transformation model for 3D MRI image harmonization. The model identifies the nonlinear mapping between MRI images of different magnetic strengths and eliminates the need for paired training images. The results were confirmed using an independent dataset, demonstrating its effectiveness to improve the image consistency.

## STUDENT POSTER # 24

**EXPLORING SURGICAL MENOPAUSE EFFECTS ON RAT FOREBRAIN CHOLINERGIC CIRCUITS: IMPLICATIONS FOR THE ENDOCRINE-BRAIN INTERFACE**. Doyle RT, Pastor J, Balasubramanian KS, Verpeut J, Bimonte-Nelson HA, Newbern JM. Arizona State University; Arizona Alzheimer's Consortium.

Background: Many women experiencing menopause report symptoms of memory loss, attention deficits, and other neurocognitive impairments. The underlying neurobiological mechanisms that contribute to these cognitive changes remain poorly understood. We have shown that spatial memory impairments in female rats occur six weeks post bilateral ovariectomy (Ovx), as well as post hysterectomy (Hyst). Previous research in this rat model suggest that reductions in circulating estrogens are linked to changes in cholinergic activity in the forebrain. Basal forebrain cholinergic neurons (BFCNs) in particular project to the hippocampus, amygdala, and medial prefrontal cortex and regulate aspects of memory, attention, and cognition.

Methods: We used immunolabeling and confocal microscopy to ask whether Ovx or Hyst alters the density of key neuronal subtypes important for BFCN interactions with the medial prefrontal cortex (mPFC) in rats six weeks after surgery. We also analyzed the expression of the activity dependent protein CFOS/FOS within these neuronal subtypes to identify potential long-term changes in activity in these forebrain circuits.

Results: We did not detect a significant difference in the density of ChAT+ BFCNs or a critical target of cholinergic afferents, VIP+ GABAergic neurons, in the medial prefrontal cortex. However, surgical menopause-induced changes were observed in the proportion of neuronal subtypes that co-express FOS in the medial septum and mPFC, findings which are currently being further analyzed.

Conclusions: Our data indicate that Ovx and Hyst do not modulate the number of core neuronal subtypes within the BFCN-cortical circuit after 6 weeks in the rat, but may result in long-lasting changes in BFCN input. Additional investigation is needed to determine whether changes in activation in these neuronal subtypes contribute to the cognitive deficits associated with menopause. Nonetheless, advancing our understanding of these mechanisms will be crucial for developing targeted treatments for cognitive deficits following transitional and surgical menopause.

## STUDENT POSTER # 25

**A CNN-BASED FOUNDATION MODEL FOR EARLY DETECTION OF PRE-SYMPTOMATIC ALZHEIMER'S DISEASE**. Dumitrascu OM, Li X, Youssef A, Sobczak J, Zhu W, Saxena S, Woodruff BK, Caselli R, Wang Y. Mayo Clinic Arizona; Arizona State University; Arizona Alzheimer's Consortium.

Background: Retinal imaging and deep learning methods had been proposed to accurately classify Alzheimer's disease (AD), with the potential for translation in clinical practice for large-scale AD screening. There is a critical unmet need to develop tools to identify AD in pre-symptomatic stages. We leverage our institutional dataset of retinal color fundus photographs (CFPs) from subjects with pre-symptomatic AD and computationally advanced natural language processing models, to train and validate PreADFound, a novel BERT (bidirectional encoder representations from transformers)-style self-supervised learning convolutional neural network (CNN).

Methods: Retinal imaging and deep learning methods had been proposed to accurately classify Alzheimer's disease (AD), with the potential for translation in clinical practice for large-scale AD screening. There is a critical unmet need to develop tools to identify AD in pre-symptomatic stages. We leverage our institutional dataset of retinal color fundus photographs (CFPs) from subjects with pre-symptomatic AD and computationally advanced natural language processing models, to train and validate PreADFound, a novel BERT (bidirectional encoder representations from transformers)-style self-supervised learning convolutional neural network (CNN).Next, we used 262 macula- or optic disc-centered CFPs from our institutional cohort of subjects with intact cognition, including amyloid-positive preclinical AD (96 images, 32 subjects) and amyloid-negative controls (166 images, 56 subjects). Amyloid-positive status was defined as amyloid-PET standardized uptake value ratio centiloid cut-off > 20. Quality analysis narrowed to 87 CFPs (48 left; 39 right) from 28 preclinical AD and 149 CFPs (75 left; 74 right) from 49 controls. The two groups were matched for age, gender and ethnicity ($p>0.05$).

We randomly divided our institutional data into training and testing sets (ratio of 8:2) and employed 5-fold stratified cross validation. The model's precision to classify pre-symptomatic AD was done using quadratic-weighted Kappa, AUROC (Area Under the Receiver Operating Characteristic), and accuracy. Furthermore, we determined the features potentially distinguishing pre-symptomatic AD from controls on the generated attention heatmaps.

Results: In our institutional testing dataset, the CNN model achieved AUROC of 0.8950, 85.11% accuracy, and kappa score of 0.655 for preclinical AD classification. The attention heatmaps derived from preclinical AD CFPs pointed out retinal regions in the supero-temporal or infero-temporal vascular arcades, in the optic nerve proximity.

Conclusions: In a real-world population with intact cognition, PreADFound achieved 85.11% accuracy to discriminate pre-symptomatic AD based on retinal fundus images alone. Superior and inferior vascular arcades close to the optic nerve were highlighted as potential early AD biomarkers.

## STUDENT POSTER # 26

**SELF-SUPERVISED LEARNING FOR ALZHEIMER'S DISEASE DETECTION USING COLOR FUNDUS PHOTOGRAPHY**. Dumitrascu OM, Li X, Zhu W, Woodruff BK, Nikolova S, Sobczak J, Youssef A, Saxena S, Andreev J, Caselli R, Chen JJ, Wang Y. Mayo Clinic Arizona; Arizona State University; Mayo Clinic Rochester; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) has posed a significant medical challenge in recent years. Accurate and widely accessible screening for AD is essential to address this global health crisis. However, current biomarkers for AD are limited by high cost (e.g., positron emission tomography), invasiveness (e.g., lumbar puncture), and the need for further validation (e.g., blood-based biomarkers). The retina offers a unique opportunity to study central nervous system disorders. Deep learning advancements have enabled automated analysis and interpretation of retinal fundus images. Given the limitations of supervised learning in medical imaging, self-supervised learning has emerged to tackle these issues. We employed a self-supervised learning technique based on the BERT method, utilizing a large amount of unlabeled retinal fundus images for pretraining, and applied this model to AD classification.

Methods: We used 178,803 retinal fundus images from the UK Biobank database for pre-training from 87,245 participants, 553 from AD patients (containing 1136 photos) and 86,692 from non-AD patients (containing 176,392 photos). We uniformly resized all photos to 224x224 and pre-trained them through the SparK framework using our previously developed CNN network (NN-MobileNet). We masked all images with 60% of the region, extracted the representational features of the retinal images by sparse convolution, and restored the images using a lightweight UNet decoder, and finally optimized the model weights using the mean square error (MSE) as a loss function.

After obtaining the pre-training weights, we started the detection task for AD patients. To ensure the quality of the retinal images, we manually selected images with good quality. The total of 362 good quality images were selected from 230 AD patients, including 169 left eye images and 193 right eye images. In addition, a total of 389 best-quality images were selected as the reference group from 282 non-AD subjects, which included 170 left-eye images and 219 right-eye images. We randomly divided the data into training and validation sets in the ratio of 8:2 and performed 5-fold hierarchical cross-validation on the dataset. Model evaluation metrics include quadratic weighted kappa, area under the receiver operating characteristic curve (AUROC), sensitivity, specificity, and accuracy. In addition, we used heat maps to confirm biomarkers in the AD and non-AD groups.

Results: In our experiments on the UK Biobank dataset, our model achieved 98.22% accuracy with a kappa score of 0.9652 and an AUC of 0.9967 for AD classification. In addition, the generated attention heatmap showed that the heatmap for AD patients specifically emphasized the small retinal vascular branches, the regions with the highest correlation with model decisions.

Conclusions: This proof-of-concept study shows that our method on retinal color photographs alone can screen for symptomatic attention deficit disorder with high accuracy. This method is expected to be applied to routine clinical practice. To address the economic burden associated with AD, future research should promote the application of our method to a larger population and investigate its cost-effectiveness for bedside screening in settings with limited medical specialists and infrastructure.

**STUDENT POSTER # 27**

**ENDOTHELIAL ACTIVATION IS ASSOCIATED WITH HIPPOCAMPAL ATROPHY IN PARTICIPANTS WITH ASYMPTOMATIC EXTRACRANIAL CAROTID ARTERY DISEASE.**

French SR, Zahra S, Wiskoski HE, Arias JC, Khakwani KZR, Howell C, Escareno CE, Heitkamp EN, Vazquez F, Pugazhendhi A, Ally M, Culwell GC, Vitali F, Bedrick EJ, Trouard TP, Alexander GE, Weinkauf CC. University of Arizona; Arizona Alzheimer's Consortium.

Background: Extracranial carotid artery disease (ECAD) is characterized by atherosclerotic plaque buildup in the common carotid and internal carotid arteries. ECAD is a well-documented risk factor for stroke and transient ischemic attack (TIA) and is treated clinically to prevent such events. Meanwhile, increasing data suggests that asymptomatic ECAD (aECAD), defined as ECAD without a stroke or TIA in the prior 6 months, promotes cognitive decline and may increase risk for Alzheimer's and related dementias (ADRD). We hypothesize that endothelial activation may be an early mechanism responsible for this increased risk. We sought to determine if VCAM-1, a blood-based biomarker of endothelial activation, is elevated in patients with aECAD and whether it is associated with early neurodegenerative mechanisms occurring in this patient population.

Methods: We enrolled 80 adults, ages 50 to 85 with a clinical diagnosis of aECAD and/or 2+ cardiovascular risk factors from the vascular surgery and cardiology clinics in Tucson, Arizona. These study participants underwent a blood draw for serum collection and sandwich ELISA was performed to detect VCAM-1. In addition, 64 of those recruited participants also underwent 3T MRI scans with high-resolution T2-weighted images to evaluate volumes of the hippocampus and hippocampal subfields using Freesurfer software. Hippocampus and hippocampal subfield volumes were adjusted according to total intracranial volume prior to the analysis. The primary statistical analyses were performed using Spearman's rank correlation and Mann Whitney U test. In addition, we performed multiple linear regression to control for other potentially confounding variables.

Results: Our participants were split into two groups based on aECAD status. Subjects with high-grade aECAD (>70%) had significantly elevated serum VCAM-1 levels compared to those with minimal aECAD (<50%, $p=0.02$). In the subset of participants with an MRI, elevated serum VCAM-1 levels were associated with decreased hippocampal volumes, a relationship which persisted after adjusting for age, sex, and cardiovascular risk factors ($b = -0.29$, $p=0.02$). When evaluating specific hippocampal subfields, we found that this negative relationship between VCAM-1 and hippocampal volumes were mainly driven by differences in the parasubiculum, HATA, subiculum, molecular layer, and CA1 subfields ($p \leq 0.05$).

Conclusions: Serum VCAM-1 was elevated in participants who had high-grade aECAD compared to those with low-grade aECAD, which was associated with decreased hippocampal volume, which showed hippocampus subfield specificity. These data demonstrate the utility of a serum-based biomarker of endothelial activation, a potential tool in stratifying neurodegenerative risk in patients with severe aECAD. These findings also support our hypothesis that endothelial activation may provide an early mechanistic link between atherosclerotic vascular disease and neurodegeneration, although these findings are currently limited by our small sample size.

**STUDENT POSTER # 28**

**PARKINSON'S-LINKED BRAIN FEATURES IN AGING AUTISTIC ADULTS.** Galindo MV, Valdez M, Ofori E, Peterson D, Rodi A, Braden BB. Arizona State University; Arizona Alzheimer's Consortium.

Background: Autism Spectrum Disorder (ASD) is a lifelong neurodevelopmental disability, but historically, very little was known about the aging process in older autistic adults. Recent converging evidence of increased Parkinsonism has been described in this community. While some previous studies have investigated brain differences in the motor system of aging autistic adults, there is a gap in evaluating the neural signatures of Parkinsonian disease in autistic adults. The objectives were to: (1) replicate previous findings of increased self-reported parkinsonism and (2) evaluate diagnostic group and age-related differences in free-water of the substantia nigra (a progression marker of PD) and gray matter characteristics of motor control brain regions in autistic vs. matched neurotypical (NT) adults.

Methods: From a cohort of 191 participants (ASD, n=105, sex (M/F) 72/33; NT, n=86, sex (M/F) 51/35) across a broad age range (ages 18-71) FreeSurfer was used to calculate left and right precentral cortical thickness and caudate, putamen, and cerebellar volumes, corrected for total intracranial volume (TIV) from T1-weighted MRIs. Additionally, in 111 participants (ASD, n=61; NT n=50), diffusion tensor imaging (DTI) scans were used to calculate substantia nigra free-water. Lastly, 67 participants (ASD n=34; NT n=33) completed the Parkinsonism Screening Questionnaire (PSQ). All analyses controlled for sex and age.

Results: See figure 1 for graphical depictions and full statistical results. Using ANCOVA, there was a significant diagnosis effect in the PSQ total, indicating that the ASD group reported higher PSQ scores vs. the NT group. Exploratory correlations showed that age and PSQ scores did not correlate in the ASD group, but a positive correlation approached significance in the NT group (Fig. 1a). Free-water in the substantia nigra right posterior region demonstrated a diagnosis effect with greater (i.e. worse) free-water in the ASD group vs. the NT group. Exploratory correlations revealed a significant positive free-water/age relationship within the ASD group while the NT group approached significance (Fig. 1b). For the caudate, the diagnosis effect reached significance on the left and approached significance on the right side with the ASD group having larger volumes vs. the NT group. The group by age interaction is significant in the left caudate, where the relationship between age and volume showed a steeper negative slope in the ASD group vs. the NT group (Fig. 1c). No other regions showed significant differences between ASD and NT groups.

Conclusions: We replicate previous findings of increased self-reported parkinsonism and larger caudate volumes in autistic adults compared to NT adults. We present novel findings of increased substantia nigra free-water (a progression marker of PD) in autistic vs. NT adults. Age correlations highlight that: 1) unlike NT adults, younger and older autistic adults are experiencing similar levels of parkinsonism, and 2) substantia free-water may be increasing more with age. Lastly, we observed a strong negative relationship between age and caudate volumes in autistic adults, suggesting that the caudate may age faster in comparison to NT adults. Analyses are in progress to confirm these findings in a longitudinal sample and determine if these brain differences may be useful biomarkers for Parkinsonism in autistic adults.

**STUDENT POSTER # 29**

**ADMINISTRATION OF ISOFORM-SELECTIVE INHIBITOR OF HEAT SHOCK PROTEIN 90-BETA AMELIORATES MEMORY LOSS AND NOCICEPTIVE BEHAVIOR IN 8-MONTH-OLD 5XFAD MICE**. Gratreak BDK, Seekins CA, Serwetnyk S, D'Amico T, Blagg BS, Streicher JM. University of Arizona; University of Notre Dame; Arizona Alzheimer's Consortium.

Background: Here, we report the reversive arm of our studies to modify tightly evolutionarily conserved molecular chaperone protein networks that are closely tied to systemic immunological processes by selectively inhibiting a specific isoform of Heat Shock Protein 90 (Hsp90) in transgenic 5xFAD mice. Non-selective pan-Hsp90 inhibitors are robustly effective in treating AD via anti-inflammatory immune modulation of microglia signaling but were halted in clinical use by toxic side effects. Studies suggest toxicity of pan-Hsp90 inhibitors is driven mostly by effects of Hsp90α inhibition. Our lead compound is >333 fold selective for Hsp90β over Hsp90α and can selectively inhibit Hsp90β while skirting Hsp90α inhibition, thus we predict being able to achieve similar benefits with fewer side effects. We hypothesized that selective Hsp90β inhibition will reduce AD pathology in the 5xFAD mouse model by immune modulation, specifically by decreasing inflammatory microglial activation, and report immunohistochemical findings here. In addition, our previous studies show that Hsp90β-selective inhibition enhances morphine pain relief, a salient opioid dose-reducing bonus in this patient population.

Methods: Six-month-old female and male 5xFAD mice were treated daily by subcutaneous injection of our Hsp90β inhibitor NDNB-01 (1mg/kg) for nine weeks and tested with biweekly open field tests (OFT), novel object recognition (NOR) tests, and overnight nestbuilding assays and additional Morris Water Maze (MWM), tail flick, Hargreaves, and Elevated Plus Maze (EPM) testing.

Results: Our previous pilot data in younger mice suggested Hsp90β inhibition conferred a significant cognitive benefit in long-term 7-day retention NOR testing at thirteen weeks of treatment. Here, we describe effects in older 5xFAD mice with higher beta-amyloid loads, whereby Hsp90β inhibition enhanced 24-hr spatial memory in MWM, ameliorated cognitive changes in OFT and EPM, improved nest-building, and restored thermal nociception via Hargreaves testing.

Conclusions: These results show that specific inhibition of the Hsp90β isoform can improve spatial and recognition memory and restore thigmotaxic and thermal pain behavior to control/vehicle levels in treated 5xFAD mice. We expect to achieve efficacy in treating AD pathology by modifying these tightly evolutionarily-conserved molecular chaperone protein networks which are closely tied to systemic immunological processes without the historically limiting side effects of Hsp90α isoform inhibition. However, a full toxicology panel is pending confirmation.

## STUDENT POSTER # 30

**CONTINUAL SKILL AND TASK LEARNING VIA DIALOGUE**. Gu W, Kondepudi N, Huang L, Gopalan N. Arizona State University; Arizona Alzheimer's Consortium.

Background: Elder care has long been an important application of automation and robotics. Recent robot systems have displayed promising results on learning and performing tasks. However, these systems are still far from being applicable in everyday scenarios. This is because it is impossible to equip these systems with all the skills and knowledge required to perform unique tasks for different users at the beginning, and these systems do not have an interface to express confusion and doubts to the human users.

Methods: In this work we present a framework for robots to query and learn visuo-motor robot skills and task relevant information via natural language dialog interactions with human users. Previous approaches either focus on improving the performance of instruction following agents, or passively learn novel skills or concepts. Instead, we used dialog combined with a language-skill grounding embedding to query or confirm skills and/or tasks requested by a user. To achieve this goal, we developed and integrated three different components for our agent. Firstly, we propose a novel visual-motor control policy ACT with Low Rank Adaptation (ACT-LoRA), which enables the existing state-of-the-art Action Chunking Transformer model to perform few-shot continual learning. Secondly, we develop an alignment model that projects demonstrations across skill embodiments into a shared embedding allowing us to know when to ask questions and/or demonstrations from users. Finally, we integrated an existing Large Language Model (LLM) to interact with a human user to perform grounded interactive continual skill learning to solve a task.

Results: Our ACT-LoRA model learns novel fine-tuned skills with a 100% accuracy when trained with only five demonstrations for a novel skill while still maintaining a 74.75% accuracy on pre-trained skills in the RLBench dataset where other models fall significantly short. We also performed a human-subjects study with 8 subjects to demonstrate the continual learning capabilities of our combined framework. We achieve a success rate of 75% in the task of sandwich making with the real robot learning from participant data demonstrating that robots can learn novel skills or task knowledge from dialogue with non-expert users using our approach.

Conclusions: This work is an important step towards applying robots in everyday scenarios, and such applications are helpful for people with cognitive impairment. For example, people with cognitive impairment can have difficulty performing long tasks because it requires people to plan and keep long concentration in their mind, and an automatic robot system can free users from these tasks. We plan to conduct additional studies with the adult population with mild cognitive impairment to understand the performance of our framework with the target user group.

## STUDENT POSTER # 31

**CARDIOMETABOLIC RISK MEDIATES THE ASSOCIATION BETWEEN PERCEIVED STRESS AND EPISODIC MEMORY SIMILARLY AMONG HISPANIC/LATINO AND NON-HISPANIC WHITE INDIVIDUALS**. Guareña L, Huentelman MJ, Ryan L. University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Cognitive health disparities have been reported, yet mechanisms by which minoritized groups are differentially impacted by poorer cognitive outcomes remains to be well understood. Compared to non-Hispanic (NH) Whites, Hispanics/Latinos experience a myriad of disadvantages such as higher rates of chronic stress, cardiovascular and metabolic diseases. Yet, research investigating the influence of stress and cardiometabolic disease on cognition in this group is very limited. The objective of the present study is to evaluate the associations between perceived stress, cardiometabolic risk, and episodic memory, and to assess whether these associations differ between Hispanics/Latinos and NH Whites.

Methods: Cross-sectional data were obtained from the MindCrowd longitudinal observational online study from age, sex, and education matched Hispanics/Latinos (n=91) and NH Whites (n=95). Participants completed the Perceived Stress Scale, a paired associates learning and memory (PALM) online task, and reported on demographic, health, and disease factors. Controlling for age, linear regression models were built to investigate the effects of perceived stress, cardiometabolic risk and race/ethnicity on total PALM scores. Mediation analysis was implemented to test the effect of perceived stress on PALM scores through cardiometabolic risk.

Results: Hispanics/Latinos performed marginally worse on the PALM task than their NH White counterparts. After controlling for age, higher perceived stress was associated with poorer PALM scores across both racial/ethnic groups. Mediation analysis revealed that higher perceived stress was associated with higher cardiometabolic risk, which in turn, was associated with lower PALM scores. Importantly, the association between perceived stress, cardiometabolic risk, and PALM scores were not different between racial/ethnic groups.

Conclusions: Perceived stress and cardiometabolic risk factors may increase susceptibility for poorer learning and memory outcomes, irrespective of race/ethnicity. Interventions to improve cognitive health might benefit from reducing stress and cardiometabolic conditions. Further research is necessary to elucidate factors contributing to cognitive disparities among Hispanics/Latinos.

## STUDENT POSTER # 32

**IDENTIFYING COGNITIVE SUBGROUPS IN OLDER ADULTS FROM COMMUNITY DATA VIA HIERARCHICAL CLUSTER ANALYSIS.** Hall JD, Green J, Chou Y. University of Arizona; Arizona Alzheimer's Consortium.

Background: Consensus diagnostic methods currently utilized to evaluate the cognitive status of older adults in community-based settings are considered the standard in diagnosis in research labs and clinics. However, consensus diagnostic methods have several limitations including but not limited to, clinical judgment which can vary across clinicians, time, and collection sites. Previous research utilizing data-driven, hierarchical, cluster-based analysis has produced reliable sub-groups of AD and MCI in large-scale community-based data that have reported stronger correlations among factors of cognition, AD biomarkers, and risk for dementia than groups classified with the consensus diagnostic method.

Methods: Participants were 202 individuals (mean age = 68.2 years [SD = 6.6]; mean education = 16.4 [SD = 2.4]; 62.8% female; 98.9% white; 94.5% non-Hispanic/Latino) with neuropsychological test scores in the NACC Uniform Data Set (UDS). Data were collected from 2020 through 2024 at one collection site. Participants were given initial consensus diagnosis classifications of CN, MCI, aMCI, or AD. Participant raw scores from neuropsychological measures were calculated and converted to z-score (age, gender, and ethnicity). Then, a hierarchical Ward-cluster analysis was performed on the converted scores to create data-driven clusters. The UDS neuropsychological tests examined in the current report included measures of memory (Immediate and Delayed Recall from Logical Memory or Craft Story), attention/working memory (Forward and Backward Digit Span or Number Span), processing speed/executive functioning (Trail Making Test, Parts A and B), and language (Category Fluency [animals, vegetables], Boston Naming Test [BNT] or Multilingual Naming Test [MINT]).

Results: This dataset and subsequent analysis produced 5 independent sub-groups (k = 5): (1) Optimal CN (48.51%) (2) Typical CN (3.47%) (3) Normal-to-mild cognitive impairment (18.32 %) (4) Mild cognitive impairment (27.72%) (5) Mild-to-moderate cognitive impairment (1.98%).

Conclusions: These results reveal data-based hierarchical cluster analysis as a promising supplement in evaluating the cognitive status of older adults in community-based settings. While the sample size in this report is small, larger-scale studies have found similar results, suggesting that this method is useful in both large clinical studies and smaller sample sizes. Future studies should consider the utilization of data-driven hierarchical cluster-based analysis of the cognitive status of older adults in community-based settings. Overall, data-driven, cluster-based, hierarchical analysis may identify more heterogeneous groups within consensus diagnoses classifications which can be helpful in the early identification of declining cognition, identifying risk of further cognitive decline, symptom management, and potential treatment of neurodegenerative diseases such as AD.

**STUDENT POSTER # 33**

**TREATMENT WITH PSILOCYBIN ALLEVIATES APPROACH-AVOIDANCE BEHAVIOR IN AGED MICE.** Hanson T, Lifshitz D, Law O, Hays A, Flores B, Olive MF, Mennenga SE, Lewis CR. Arizona State University; University of Arizona, College of Medicine-Phoenix; Arizona Alzheimer's Consortium.

Background: Classic psychedelic drugs, such as psilocybin, are emerging novel therapies for brain-related conditions due to their well-characterized effects on increasing neuroplasticity. Recent animal models demonstrate both anxiolytic- and antianhedonic-like effects of classic psychedelics in young adult animals. However, the effects of psilocybin on age-related cognitive and behavioral decline have not yet been studied. For this study, we hypothesize that psilocybin treatment in aged animals will attenuate age-related cognitive decline as well as anxiety-, and depressive-like behaviors.

Methods: Aged C57BL/6 mice were group housed on a reverse light cycle and given food ad libitum (N=78, 47% female; 11-13 months of age). Animals were administered either 1mg/kg of psilocybin or saline 1/week for 2 weeks. Three days after the last treatment, animals underwent behavioral testing to assess cognition, anxiety-like, and depressive-like behaviors. Behavioral measures for anxiety- and depressive-like behavior included a 5-minute trial assessing novelty-suppressed feeding 7 days post-treatment, and a 10-minute marble burying 14 days post-treatment.

Results: Results indicate a significant effect of Treatment ($F(1,73)=4.74$, $p=0.03$) and a marginal Treatment x Sex interaction ($F(1,73)=2.79$, $p=0.10$) on novelty-induced latency to feed, with psilocybin-treated mice showing reduced latency to feed compared to controls, and a larger effect in males than females. A sex difference was found in the marble burying task ($F(1,77)=7.20$, $p=0.009$), with females burying more marbles than males, but psilocybin treatment did not affect number of marbles buried in either sex.

Conclusions: Results are consistent with prior literature demonstrating psilocybin sex-specific anti-anhedonic effects after chronic, variable stress. Here, we report for the first time that these clinically relevant psilocybin effects can be extended to aged animals.

## STUDENT POSTER # 34

**ALZHEIMER'S DISEASE GENETIC RISK DOSAGE IN AUTISTIC INDIVIDUALS.** Harker SA, Piras I, Huentelman MJ, Taguinod F, Lewis CR, Braden BB. Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Middle-aged and older autistic adults are more likely to be diagnosed with early onset Alzheimer's disease (Alz) compared to neurotypical adults. Despite known lifelong challenges, understanding of cognitive and brain aging with ASD is lacking. Recently, we were the first group to publish longitudinal cognitive and brain aging findings in older autistic adults which identified accelerated memory decline and hippocampal volume loss. Genetics explain substantial variance in cognitive aging outcomes and incidence of neurodegenerative disease, but there are no genetically-informed studies of aging with ASD. Our group and others have found that autistic individuals are more likely to carry the apolipoprotein E (APOE) ε4 allele, the strongest genetic risk for Alz, than neurotypical populations. Building upon these prior findings, this study tested the hypothesis that autistic adults carry a higher cumulative genetic risk for Alz, known as a polygenic risk scores (PRS), compared to neurotypical adults.

Methods: Participants were recruited through our ongoing, well-characterized longitudinal cohort of autistic adults (without intellectual disability) and matched neurotypical controls, who receive cognitive and MRI batteries every two-years (n=121, ages 40-75, mean=55.2 years; M:F ratio 1.6:1). DNA extracted from saliva was genotyped on the Illumina Global Diversity Array with an additional 180K neurodegenerative disease markers, then imputed for whole genome coverage through the TOPMed server. PRS was generated from a GWAS of 71,880 Alz and 383,378 controls. We used various p-value thresholds to select GWAS variants for the PRS to determine the optimal procedure. ANCOVA was used to test a diagnostic group difference in Alz PRS, controlling for sex, the interaction between group and sex, and 10 ancestry components.

Results: For all p-value thresholds, the ASD group had a larger Alz PRS mean compared to controls, however the group difference reached significance for the 1e-08 threshold (p=0.0344). The threshold of 1e-08 produced PRS scores that explained the most variance in our model, as measured by the R2 value (R2 = 0.122). Whereas a threshold of 1e-04 appears too lenient, as the R2 value decreased (R2 = 0.069).

Conclusions: Because we used a relatively small sample for these analyses, we are currently seeking publicly available data to improve our power. Further, we will evaluate if the Alz PRS score mediates age-related accelerated cognitive decline in autistic adults.

## STUDENT POSTER # 35

**A NOVEL SCORING PROTOCOL FOR ASSESSING UNPROMPTED IMAGINATIVE THINKING IN YOUNG AND OLDER ADULTS.** Hovhannisyan M, Grilli MD, Andrews-Hanna JR.
University of Arizona; Arizona Alzheimer's Consortium.

Background: Our recent framework proposes that distinct component processes referred to as the "mind's eye" (concrete, image based-form of imagination) and the "mind's mind" (abstract, verbal-based form of imagination) are supported by subsystems of the default network and unite to form the basis of imaginative thinking (Andrews-Hanna & Grilli, 2021; Raffaelli et al., 2020). Here, we aim to uncover age-related differences in cognitive biases for these different forms of imagination by employing our recently developed scoring protocol (Hovhannisyan et al., submitted) to a "think aloud" rest paradigm designed to capture unprompted imaginative thinking. We explored two alternative hypotheses supported by the literature. On the one hand, a higher mind's mind vs. mind's eye bias might be observed in older adults considering our previous work (Hovhannisyan et al., submitted) showing such age-differences during autobiographical remembering. On the other hand, similar cognitive biases might be observed across age groups, considering our recent review of the literature noting overall weak evidence for age-related differences in default network subsystem functional engagement in normal versus pathological aging (Andrews-Hanna et al., 2019).

Methods: Participants were 43 young and 44 older adults, neuropsychologically screened to ensure normal cognition. Participants completed the "think aloud" paradigm at home over Zoom Health. They were asked to speak aloud the contents of their conscious experience across a ten minute unprompted rest period. To capture the distinction between the mind's eye and mind's mind, we applied our novel scoring protocol to transcribed audio files.

Results: A two-way group (young vs older) by imagination type (mind's eye vs. mind's mind) mixed analysis of variance revealed that there was an overall bias toward the mind's eye during a period of unprompted imaginative thinking, $F(1,85) = 41.3$, $p < 0.001$. However, there was not a significant main effect of age group on overall content generated, $F(1,85) = 1.007$, $p = .32$, and there was no significant interaction between age group and the relative use of the mind's eye and mind's mind, $F(1,85) = 2.69$, $p = 0.11$. A follow-up Bayesian mixed analysis of variance revealed substantial evidence of no overall age group difference, $BF10 = .19$, and no interaction between age group and imagination type, $BF10 = 0.14$.

Conclusions: We found that during unprompted thought, participants exhibited an overall bias toward their use of the mind's eye (versus mind's mind) and that this bias did not significantly vary between age groups. These findings align with prior research comparing default network engagement between young and older adults during prompted versus unprompted imaginative thinking. If replicated, these preliminary findings suggest that the context with which imaginative thoughts are assessed (e.g., deliberately retrieving past events versus thinking in an experimentally unconstrained manner) might contribute to different manifestations of the mind's eye and mind's mind in older adults compared to young adults, which might have implications for understanding and testing normal and abnormal aging.

## STUDENT POSTER # 36

**PERFUSION AND CEREBROVASCULAR REACTIVITY CHARACTERIZATION IN ALZHEIMER'S DISEASE AND VASCULAR DEMENTIA.** Keeling EG, McElvogue MM, Ott LR, Burke AD, Sabbagh MN, Bakkar N, Stokes AM. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: Cerebrovascular changes are often reported in normal aging, Alzheimer's disease (AD), and vascular dementia (VaD). Cerebral perfusion and cerebrovascular reactivity (CVR) both decrease with dementia compared to healthy aging; as these changes occur prior to symptomatic onset and in distinct brain regions, perfusion and CVR may act as complementary biomarkers of early cerebrovascular changes. These biomarkers can be measured using MRI methods, yielding measures of perfusion and CVR sensitive to total vasculature. We recently developed a more advanced method capable of measuring microvascular-specific measures of perfusion and CVR. Here, we characterized the cerebrovascular profiles of AD and VaD using complementary perfusion and CVR biomarkers representing both total and microvascular regimes.

Methods: MRI data were acquired at 3T (Ingenia, Philips) in three cohorts: non-cognitively impaired cohort (HC, n=8, 6 females), AD (n=7, 3 females), and VaD (n=4, 2 females). Functional MRI (fMRI) data were acquired with a multi-echo, multi-contrast (SAGE) acquisition (5 echoes (TE), 8.0/27/59/78/97 ms) and the following acquisition parameters: TR=3.0 s, voxel size = 3×3×3 mm, 160 volumes, acquisition time = 8 min. SAGE perfusion data were acquired before, during, and after injection of gadolinium-based contrast agent. Acquisition parameters include: TE1-5 = 7.7/26/56/74/92 ms, repetition time (TR) = 1.5 s, voxel size = 2.75×2.75×5 mm, 200 volumes, acquisition time = 5 min. SAGE data underwent standard pre-processing. Echo-combined images, as well as total and microvascular cerebral blood flow (CBF), cerebral blood volume (CBV), and relative CVR (rCVR), were calculated using advanced analysis pipelines. Standard T1-MPRAGE and T2-FLAIR high-resolution structural images were acquired and used for tissue segmentation into normal-appearing gray (NAGM) and white matter (NAWM) and white matter hyperintensities (WMH). The Montreal Cognitive Assessment (MoCA) was administered prior to MRI acquisition. Kruskal-Wallis and Dunn tests were performed to assess group and pairwise differences for age, MoCA score, CBF, CBV, and rCVR within each tissue type (FDR correction for multiple comparisons).

Results: Age was significantly higher for the AD group than HC ($p=0.017$), and MoCA scores were significantly lower for AD compared to HC ($p=0.0025$). CBF was significantly higher in HC than AD in NAGM (total: $p=0.049$, microvascular: $p=0.042$) and WMH (total, microvascular: $p=0.036$). CBF in HC was also significantly higher than VaD in NAGM (total: $p=0.049$, microvascular: $p=0.042$) and WMH (total, microvascular: $p=0.048$). WMH CBV was higher in HC than AD (total: $p=0.066$, microvascular: $p=0.077$) and VaD (total: $p=0.089$). NAWM CBF was higher in HC than AD (total, microvascular: $p=0.058$) and VaD (total, microvascular: $p=0.058$). There were no significant differences in rCVR between groups.

Conclusions: Total and microvascular perfusion decreases with AD and VaD. Enrollment is ongoing, and future directions include analysis of perfusion metrics within cortical and subcortical regions and correlation of neuroimaging findings with cognitive testing.

**STUDENT POSTER # 37**

**AGE AND APOE ASSOCIATED TRAJECTORIES FOR PLASMA-NFL AND CORTICAL THICKNESS IN PRE-CLINICAL ALZHEIMER'S DISEASE.** Kira K, Malek-Ahmadi M, Su Y, Ghisays V, Luo J, Devadas V, Chen Y, Lee W, Protas H, Chen K, Zetterberg H, Blennow K, Caselli RJ, Reiman EM. Arizona State University; Banner Alzheimer's Institute; University of Gothenburg; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Plasma NfL is a predictive maker of cognitive decline and neuroimaging measures of neurodegeneration. The APOE epsilon4 allele is associated with increased brain amyloid and an increased risk of developing AD. It is also associated with decreased hippocampal volume and decreased memory performance across the AD. Alzheimer's Disease typically damages the parts of the brain that involves memory, language, reasoning, and social behavior. Some of these regions include the hippocampus and entorhinal cortex, frontal lobe, parietal lobe, temporal lobe. In our study we used the following Regions of Interest (ROI): hippocampus volume, entorhinal thickness, para-hippocampal thickness, precuneus thickness and temporal pole thickness. The aim of this study was to determine the age- and APOE epsilon4-associated trajectory of plasma NfL and MRI based measures of neurodegeneration in cortical ROI.

Methods: Data from cognitively unimpaired (CU) participants in the Arizona APOE Cohort were used for this analysis. A total of 151 participants' samples were taken and among them, about 72% were female and the average age at first NfL measurement was 62.36±6.35. The average length of follow-up was 6.43±2.91 years. APOE ε4 genotype prevalence was 52% (n =79) for Non-Carriers (NC), 30% (n =45) for Heterozygotes (HT), and 18% (n =27) for Homozygotes (HM). Cortical thickness measures using FreeSurfer 6.0 default Desikan-Killiany atlas. Linear mixed effects models that adjusted for age at first plasma-NfL measurement, sex, and education were used to derive annualized change values for plasma NfL, hippocampal volume, entorhinal cortex thickness, parahippocampal thickness, precuneus thickness, and temporal pole thickness.

Results: Only the annualized plasma-NfL change for HT remained significantly greater than NC change after adjusting for age, sex, and education. HT decline in temporal pole thickness, and hippocampal volume was significantly greater than NC decline after adjusting for age, sex, and education. Decline in entorhinal cortex thickness, parahippocampal thickness and precuneus thickness was not significantly different after adjusting for age, sex, and education.

Conclusions: Plasma NfL begins to increase in heterozygote patients around the age of 62 and starts to increase in homozygote patients around the age of 72. There is also a linear steady increase in non-carriers as plasma NfL and age increases. Hippocampal volume follows a similar trajectory as that of plasma NfL. Except for the entorhinal cortex thickness, all other brain regions follow a similar pattern. The only difference is they are mostly around 0, regarding the carriers. Around the ages of 65-72 there is an increase in neurodegeneration in hetero and homozygotes compared to non-carriers.

**STUDENT POSTER # 38**

**THE ROLE OF CARDIOVASCULAR BURDEN ON EXECUTIVE FUNCTIONING AND PROCESSING SPEED PERFORMANCE IN A COGNITIVELY NORMAL SAMPLE.** Krall D, Malek-Ahmadi M, Blake L, Auman B, Belden CM, Atri A, Arch R, Serrano G. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: With cerebrovascular disease being the second leading cause of dementia, neurocognitive decline associated with cardiovascular risk factors has garnered substantial attention in research. Current literature shows associations between cardiovascular risk factors (e.g., hypertension, diabetes) in midlife and later life development of cognitive impairment (i.e., vascular cognitive impairment; VCI) or dementia (i.e., vascular dementia; VaD). Neuropsychologically, VCI and VaD have been associated with deficits or impairments in executive functioning and processing speed. However, there remains a lack of research evaluating cognitive functioning among cognitively normal individuals in later life with underlying cardiovascular risk factors. The current study investigated the relationship between cardiovascular burden and cognition in a cohort of individuals without known cognitive impairment.

Methods: This study utilized measures of executive functioning (Stroop Color/Word; Trails B; Digit Span Backwards) and processing speed (Stroop Word; Stroop Color; Trails A; WAIS-R Digit Symbol) in a group of consensus-conferenced deemed cognitively normal adult participants enrolled in the Brain and Body Donation Program (BBDP; n=317) at Banner Sun Health Research Institute (BSHRI). Cardiovascular burden was defined as the number of cardiovascular-related medical conditions (i.e., risk factors) reported in the subject's health/ medical history. Cardiovascular risk factors included hypertension, hypercholesterolemia, diabetes, atrial fibrillation, angioplasty, history of myocardial infarction, past/present cigarette use, cardiac bypass, and congestive heart failure. Pearson correlation was used to assess the association between the cardiovascular burden score and cognition. These associations were further examined using linear regression models that adjusted for age, sex, and education. Finally, ANOVA analyses was used to assess differences in executive function and processing speed between those with or without each cardiovascular risk factor.

Results: Regression analyses indicated a small, but statistically significant relationship between cardiovascular burden and executive functioning scores ($r = -0.11$, $p < 0.05$), as well as processing speed scores ($r = -0.14$, $p = 0.01$). These associations remained significant after adjusting for age, sex, and education. Findings from the ANOVA revealed no significant between-group differences ($p= 0.84$).

Conclusions: Cardiovascular burden was significantly negatively associated with performance on executive functioning and processing speed tasks. These findings are consistent with previous research suggesting that cardiovascular risk factors have an adverse impact on processing speed and executive functioning. No significant between-group differences were revealed, indicating that individual/specific cardiovascular risk factors did not account for significant changes in cognitive functioning. Consistent with prior research, specific risk factors do not appear to pose inherent risk to cognitive decline, but rather the culmination of cardiovascular burden poses increased risk on one's cognitive well-being. Future research should aim to continue evaluating the relevance of specific cardiovascular risk factors in their relationship to cognitive performance.

## STUDENT POSTER # 39

**CHARACTERIZATION OF ALZHEIMER'S DISEASE-RELATED NEURO-INFLAMMATION UTILIZING A 5XFAD MOUSE MODEL.** Leslie A, Reyes-Reyes E, Rodgers K. University of Arizona; Arizona Alzheimer's Consortium.

Background: Alzheimer's Disease (AD) is a progressive neurodegenerative disorder that is the cause of 60-70% of dementia cases in the United States. The hallmarks of AD include amyloid plaques, neurofibrillary tangles, and the loss of neuronal connections. This results in atrophy of brain tissues and inflammation. Current research studies use transgenic mouse models to understand the development and progression of AD over time.

In this study, we used a 5xFAD mouse model which overexpress: (1) mutant human amyloid beta precursor protein AD mutations and (2) human presenilin 1 AD mutations. The objective of this study is to characterize neuroinflammation using this model and investigate the progression of AD. This will help determine the time frame in which therapeutics may be effective.

Methods: A total of forty 5xFAD mice were used in this experiment. Five female and five male mice were sacrificed at 5 weeks, 2 months, 5 months, and 7 months of age. The tissues collected from each mouse included the brain, meninges, blood, and spleen. The right brain and meninges underwent cell dissociation to be stained for flow cytometry. Then, white blood cells were isolated and stained for flow cytometry as well. Cells were quantified and characterized using Flow Logic. Then, data analysis was done using GraphPad Prism 10.

Results: Preliminary results of the study show that there is an increase of microglial and astrocytic communication over each timepoint for both females and males. Also, white blood cells expressed a significant increase of neutrophils and monocytes from 2 months to 5 months of age among both sexes.

Conclusions: In conclusion, these results display an increase of neuronal and peripheral inflammation. These indications could also reflect dysfunction of the blood brain barrier.

**STUDENT POSTER # 40**

**TREATMENT WITH PSILOCYBIN ALLEVIATES APPROACH-AVOIDANCE BEHAVIOR IN AGED MICE.** Lifshitz D, Hanson T, Law O, Hays A, Flores B, Olive MF, Mennenga* SE, Lewis* CR. Arizona State University; Arizona Alzheimer's Consortium.

Background: An estimated 40% of individuals will experience some cognitive decline after the age of 65. Although most pharmaceutical research to date has focused on drug development to prevent or treat dementia, interest is growing in utilizing classic psychedelic drugs, such as psilocybin, as a potential therapy for age-related cognitive decline. These drugs have shown a well-characterized ability to increase neuroplasticity and induce acute therapeutic effects that last beyond drug elimination, lending them as a promising novel therapy. Though recent preclinical studies have demonstrated both the anxiolytic and antianhedonic effects of these drugs, their impact on age-related cognitive outcomes has not yet been researched.

Methods: This study seeks to test the hypothesis that psilocybin treatment will reduce symptoms of cognitive aging in aged mice. C57BL/6 mice were group-housed on a reverse light cycle and given food ad libitum (N=78, 47% female; 11-13 months of age). Animals were injected with either 1mg/kg of psilocybin or saline 1/week for 2 weeks. Three days post-injection, animals performed a habituation and three test trials of a water Y-Maze task over four days.

Results: Preliminary results show that psilocybin treatment did not affect female mice's cycling (they cycled regularly throughout the duration of the study) or body weights ($F(1,154)= 0.083$, $p= 0.77$, NS). Furthermore, males outweighed females ($F(1,154)= 32.005$, $p<0.001$) and received higher body-weight-based doses of psilocybin ($F)1,154)= 8.65$, $p=0.004$).

Conclusions: All data has been collected and is awaiting further analysis, which will be presented at our poster session during this conference. Full conclusions have not been drawn, as more in-depth results are being analyzed currently.

**STUDENT POSTER # 41**

**RISK FACTORS ASSOCIATED WITH MILD COGNITIVE IMPAIRMENT AMONG MEXICAN IMMIGRANT ADULTS IN SOUTHERN ARIZONA**. Lindemer SL, Maldonado A, Ochoa Mora E, Gonzalez AS, Villavicencio EA, Garcia DO. University of Arizona; Arizona Alzheimer's Consortium.

Background: While much literature is available on Mild Cognitive Impairment (MCI) among non-Hispanic whites, little research exists among Mexican immigrant populations. This is a significant gap in the literature as Hispanics are one of the fastest-aging segments of the U.S. population. With estimates indicating that the Hispanic population aged 65 and older is projected to grow to 20 million by 2060, there is a significant need for research aimed at identifying those with MCI. Therefore, this study was undertaken to provide a characterization of risk factors associated with MCI among Mexican immigrant adults in Southern Arizona.

Methods: Data were collected from a community-based sample of 192 Mexican immigrant adults (women = 135; men = 57; mean age = 52 ± 12 years) residing in the Southern Arizona U.S./Mexico border region. The Montreal Cognitive Assessment in Spanish (MoCA-S) was administered to each participant by a trained assessor. MoCA-S assessments were scored according to established guidelines, and a total score was calculated by summing the scores across all domains (i.e., visuospatial abilities, attention, language, abstraction, delayed recall, and orientation). A higher total score indicates better cognitive performance. MoCA-S scores were interpreted based on established cutoffs for MCI and normal cognitive function. The following ranges are used to grade severity: 26-30 (normal cognition), 18-25 (mild cognitive impairment), 10-17 (moderate cognitive impairment), and <10 (severe cognitive impairment). A generalized linear model was fitted to explore the determinants of MCI while adjusting for sociodemographic characteristics.

Results: The mean MoCA-S score was 21.6 ± 3.9, ranging from 9.0 to 29.0, with 130 participants (66.3%) being identified with mild cognitive impairment. Neither sex nor age differences on MCI were observed ($p > 0.05$). Obesity, non-alcoholic fatty liver disease, high cholesterol, hypertension, diabetes, perceived stress, and sociodemographic characteristics were not associated with MCI ($p > 0.05$). However, risk for clinical depression (CES-D score ≥ 16; $b = 1.54$, $SE = 0.69$, $p = 0.03$) and educational attainment ($b = 0.82$, $SE = 0.58$, $p < 0.001$) were associated with MCI. Post hoc analyses showed that the mean MoCA-S score for participants at risk for clinical depression was higher compared to their counterparts ($M = 22.7 \pm 3.6$ vs. $M = 21.2 \pm 4.0$, $p = 0.02$). In addition, compared to those who completed grades 1-6 ($M = 19.1 \pm 4.7$), grade 7-8 ($M = 21.0 \pm 4.1$), grade 9-12 ($M = 22.1 \pm 4.1$), and some college education ($M = 21.4 \pm 2.7$), mean MoCA-S scores were higher for participants with a bachelor's degree or higher ($M = 24.3 \pm 2.8$, $p < 0.05$).

Conclusions: Overall, there is a high incidence of MCI among Mexican immigrants in Southern Arizona. Risk for clinical depression and educational attainment were identified as risk factors contributing to cognitive impairment. These findings have important implications for clinical and community-engaged research efforts to enhance mental health and education support to reduce the risk of cognitive impairment progression to dementia and Alzheimer's in this population.

**STUDENT POSTER # 42**

**A NOVEL PRECLINICAL TASK FOR THE ASSESSMENT OF SOCIAL RECOGNITION MEMORY UNDER VARIOUS LOAD DEMANDS.** Lizik CR, Kelley-Wolfe K, Wu ES, Asadifar S, Verpeut J, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.

Background: In socially behaving animals, the ability to recognize members of one's species on an individual basis is a critical form of memory, mediating social interactions necessary for survival. Wild rodents demonstrate social recognition memory for members of their colony, which can contain hundreds of members; in the laboratory, a variety of behavioral tasks quantify social recognition memory on the premise of novelty exploration, in which the time spent exploring a novel, never-met conspecific is greater than the time spent exploring a familiar, previously-met animal. Paradigms for the evaluation of social memory are valuable because multiple memory types can be impaired by age, but the extent to which one domain is impacted is not dependent upon another domain's trajectory. This dissociation of memory domains calls for specific cognitive assays to decipher changes with many factors of clinical relevance including aging, menopause, and ovarian hormone modulation. Available paradigms involve repeat exposure to the same individual or a binary choice between a novel or familiar conspecific. While these paradigms offer insight and value, they do not address the question of memory load, which increasingly taxes cognitive capacity as load increases. Here, we present a novel behavioral apparatus and protocol that we designed for the systematic evaluation of social memory with an increasing memory load in the rodent.

Methods: Our protocol considers and builds upon current, relevant behavioral tasks quantifying social recognition memory on the premise of novelty exploration, in which the time spent exploring a novel, never-met conspecific is greater than the time spent exploring one familiar, previously-met animal. Current paradigms evaluating social memory do not address the question of memory load, which increasingly taxes cognitive capacity as load increases. We addressed this by creating a task in which multiple conspecifics must be learned and remembered in a single trial. Additionally, we compared two versions of the protocol: one in which increases in memory load were progressive across trials (Progressive), and one in which the load challenge of each trial was semi-randomized (Non-progressive).

Results: We found that young, gonadally-intact female rats could recognize numerous conspecifics simultaneously. Specifically, rats could differentiate between one novel and one familiar, between one novel and two familiars, and between one novel and three familiars. At higher social working memory demands, recognition ability was lost. Additionally, the Progressive and Non-progressive load conditions did not yield different patterns in social recognition memory abilities.

Conclusions: Here, we introduce a novel paradigm for the study of a clinically relevant memory type, which is conserved across social species and distinct from other memory types in neurobiological and neuroendocrine underpinnings. This newly developed social recognition memory load task provides a relevant tool for the experimental evaluation of social memory across innumerable neurobiological factors and related trajectories, including but not limited to age, hormonal manipulations, sex, and neurodegenerative disease.

## STUDENT POSTER # 43

**CREATION AND TESTING OF A NOVEL FINE MOTOR TASK INTENDED FOR THE DETECTION AND ANALYSIS OF NEURODEGENERATIVE PRECURSORS.** Lukacik D, Melick A, Schaefer S, Beeman S, Verpeut JL. Arizona State University; Arizona Alzheimer's Consortium.

Background: In the United States, Alzheimer's Disease (AD) affects ~1 in 9 individuals over 65. Despite the high rates of primary care visits, with about 90% of older adults attending regularly, nearly half of all dementia diagnoses are missed (Bradford et al., 2009; Lang et al., 2017). This diagnostic challenge underscores the need for simple, affordable, and reliable tools to aid in early detection. Schaefer et al. developed the Quick Behavioral Exam to Advance Neuropsychological Screening (qBEANS), an upper-extremity motor task that can predict amyloid burden and bilateral hippocampal loss (Schaefer et al., 2020; Schaefer et al., 2022). We have created a rodent analog of qBEANS to understand the specific neurological aspects the task is sensitive to and to enhance our understanding of motor neuropathology in AD.

Methods: A clear Plexiglass chamber (27 x 12 x 22 cm) with a small (13.5 x 1.5 cm) slot was created to test reaching ability of rats in retrieving sucrose pellets (45 mg) from a bowl. A flat 3D-printed practice bowl was used for training purposes. Then, two distinct 3D-printed bowls (50 x 40 x 1.9 mm) were designed using CAD software with either no physical obstruction (plain bowl with more or less pellets) or with 3 tower obstructions (Plinko bowl). All rats were habituated for 20-min per day: day 1 with a cage mate and day 2 alone. Then, rats were trained on the practice bowl until their reaches met criteria of 3 consecutive days of 10 reaches per session (10-min sessions). Fisher (CDF) rats (n=5) were tested starting at 3 months of age. Animals were food-restricted and maintained at 90% of their initial body weight. Animals were tested for 3 days per bowl, then administered Harmaline (10 mg/kg) to induce essential tremor and retested. All trials were recorded using a high-speed video camera (216 FPS) to quantify kinematics using Social LEAP Estimates Animal Poses (SLEAP), a pose-tracking machine-learning program.

Results: Our results demonstrate that rats learned to reach within 7 days. Success rates increased over the training days within bowl type but decreased with the introduction of more challenging bowls. Bowl type significantly predicted reach failures ($p = .007$), with the number of failures per day increasing per bowl ($3.87 \pm 2.23$ to $7.8 \pm 8.90$ to $11.2 \pm 5.95$). A mixed-effects model analysis further supported these findings, showing significant effects of bowl type on reach failures ($\chi^2(2) = 9.12$, $p = .010$), indicating that the complexity of the bowls contributed substantially to the increase in reach failures. Harmaline administration significantly disrupted the total number of reaches across all bowl types (paired t-test, $t(4) = 3.02$, $p = .033$). Additionally, the success rate dropped significantly post-harmaline administration ($p = .045$).

Conclusions: The presented novel fine motor reaching task successfully incorporated multiple stages with increasing difficulty. The significant impact of harmaline-induced tremor on task performance suggests potential for detecting motor impairments associated with AD (see Melick et al. 2024 AAC poster). Future research will examine unique aspects of motor kinematics and neural mechanisms necessary for this task.

## STUDENT POSTER # 44

**A NEUROVASCULAR UNIT ON-A-CHIP MODEL FOR STUDYING THE INTERACTIONS BETWEEN BRAIN CAPILLARY NICHE AND STEM CELL-DERIVED NEURONS**. Manoharan TJM, Bamfonga G, Andrews MG, Migrino RQ, Nikkhah M. Arizona State University; Phoenix Veterans Affairs Health Care System; University of Arizona, College of Medicine-Phoenix; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD), a major neurodegenerative disease, is projected to impact nearly 13 million people in the USA by 2050. Traditional research methods rely on 2D assays and animal models which often fail to fully replicate the complexity of human brain tissue and interactions. Consequently, 3D in vitro models have gained more attention for their ability to better mimic the dynamic brain microenvironment compared to 2D models while using human or patient-derived tissue. Leveraging the use of microscale technology, this study utilizes a spatially organized three-layered microfluidic model of neurovascular unit (NVU) on-a-chip to recapitulate capillary niche blood brain barrier (BBB) and to gain foundational insights into the interactions between human stem cell-derived neurons and BBB.

Methods: The microfluidic chip model was fabricated using a soft lithography technique that features three interconnected semicircular regions: core, stroma, and vasculature. To establish BBB, primary brain endothelial cells and pericytes were mixed in fibrin hydrogel and injected into the vascular region of the chip for 7 days. Upon the formation of BBB, human iPSC-derived neurons and acellular Matrigel® were injected into the core and stroma region of the platform respectively.

Results: Initially BBB was established for 3 days and was characterized for its perfusability using real-time microbead assay. To maintain the BBB integrity post-neuron injection, two media conditions were tested. Based on the live/dead assay it was found that the 100% neuron media compromised vascular integrity, while 50% neuron 50% EGM-2-MV (50:50) mix maintained the cell viability, its integrity was lost. To further maintain the integrity of the BBB post-media switch, we extended the culture period to 7 days. Prolonging the culture period resulted in stabilized BBB formation, forming thick bundles of vascular network with open lumens, as evidenced by CD31/F-Actin staining. Finally, to assess the interaction between neurons and BBB, we assessed two conditions: (i) mono-culture of neurons and (ii) co-culture of neurons with BBB. After 7 days, F-Actin/Tuj1 staining indicated that in monoculture, neurons branched randomly throughout the stroma layer. In contrast, in coculture with the BBB, neurons extended fasciculated and elongated axonal projections oriented towards the BBB layer.

Conclusions: Overall, we demonstrated successful development of a human NVU on-a-chip model to assess the interaction of BBB and neurons. Immunofluorescent staining highlighted the distinct neuronal adaptations: random branching in mono-culture and directed neurite projections towards BBB in co-culture emphasizing the unique capability of our model system in capturing intricate cellular interactions within the brain. Future studies will utilize the proposed model to investigate the molecular perturbations promoting degeneration in AD, aiming to uncover the complex mechanisms underlying AD pathogenesis and to test potential therapeutic interventions.

## STUDENT POSTER # 45

**LYSOSOMAL DYSFUNCTION PROMOTES MICROGLIAL MEDIATED INFLAMMATION AND REDUCTION IN PGRN LEVELS.** Maqsood S, Lin J, Harrison AM, Uppalapati CK, Leyva KJ, Hull EE. Midwestern University; Arizona Alzheimer's Consortium.

Background: Alterations in lysosomal function appear early in the neuroinflammatory response associated with pathology in Alzheimer's Disease (AD). This work explores the therapeutic potential of PGRN to restore lysosomal function and reduce microglial-mediated inflammation. Evidence supporting the role of PGRN in maintaining lysosomal function and reducing pro-inflammatory cytokine production has been documented in multiple neurodegenerative disease models. Specifically, PGRN is proteolytically processed within, and promotes the function of, lysosomes and lysosomal pH determines PGRN production and processing. At the mRNA level, transcripts coding for PGRN may have altered stability due to disruptions in RNA processing associated with lysosomal dysfunction. Interestingly, 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. Thus, this work is focused on identifying the appropriately processed PGRN which has the potential to restore lysosome function, decrease inflammation, and be an effective therapeutic in AD patients.

Methods: The HMC3 human microglial cell line and primary mouse microglial cells were used to measure microglial activation and cytokine production by qPCR, immunomicroscopy, and flow cytometry. 3' UTR reporter constructs were used to assay the effects of inflammation on mRNA stability.

Results: Results support a bi-directional relationship between lysosomal function and a microglial-mediated inflammatory response. Disruption of lysosomal function with either a protease inhibitor or alkalizing agent increases production of proinflammatory cytokines by microglia. Reciprocally, treatment of microglia with IFN-gamma alkalizes lysosomes. Interestingly, dysfunctional lysosomes are associated with increased levels of complement proteins which form the pro-inflammatory complosome complex and potential wide-spread shifts in RNA processing which, in turn, appear to alter PRGN levels through miRNA mediated mechanisms.

Conclusions: Results support a central role for lysosomal function in modulating the microglial-meditated inflammatory response and suggest dysfunctional lysosomes have altered mRNA stability and processing.

**STUDENT POSTER # 46**

**HIGH RESOLUTION EX VIVO MRI REVEALS AGE-RELATED CHANGES IN BONNET MACAQUE LOCUS COERULEUS ASCENDING WHITE MATTER TRACTS.** McDermott K, Dieckhaus L, Hutchinson E B, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

Background: The locus coeruleus (LC) is a brainstem nucleus with wide projections throughout the cortex. LC ascending projections to the forebrain join the brainstem central tegmental tract (CTT), a tract in the pons that terminates in the thalamus. Cortical projections from the LC are critical for normal learning and attention, and the extent to which age-related changes in LC-forebrain projections occur has not been well studied. MRI- and DTI-based tractography analysis of the LC and its cortical projections has historically been difficult due to the small size of the LC and the amount of crossing fibers in the brainstem. However, by analyzing the projections along the CTT, a well-defined white matter brainstem tract, we have been able to overcome some of these issues and analyze the microstructure of the LC and CTT with respect to age.

Methods: We performed high resolution ex-vivo MRI on perfused whole brains of 3 adult (14-20 years) and 4 aged (28-34 years) female bonnet macaques. Scans included diffusion tensor imaging (DTI) scans with high (1500-3000,4500; 32,32,64 directions respectively) b-value shells and directions at 600μm resolution; these high b shells and angular resolution allow for better modelling of white matter tracts. Additionally, we collected scans that allow us to quantify myelin water fraction (MWF) and Bound Pool Fraction (BPF) using multi-spin echo (MSE) T2 and selective inversion recovery (SIR) T1 scans. Additionally, we collected a high resolution T2 weighted at 200μm resolution, which we used for manual segmentation of regions of interest (ROIs) such as the LC and thalamus. Probabilistic tracts from the LC to the thalamus (CTT) were modelled from the diffusion data using MRTRIX. Generated tracts were thresholded for extraction of map values such as Fractional Anisotropy (FA), Radial Diffusivity (RD), Axial Diffusivity (AD), Trace (TR), Myelin Water Fraction (MWF), and Bound Pool Fraction (BPF). These MRI metrics are derived from diffusion and relaxometry based techniques and offer insight into myelination and microstructural integrity. Additionally, local MRI was performed on a subset of the animals (6/7) by resting the whole brain on a 10mm loop coil centered around the brainstem and temporal lobes. This allowed for higher resolution analysis of the brainstem, and we re-drew LC ROIs from these scans to analyze similar metrics from the whole brain analysis.

Results: Preliminary ROI regression analyses revealed that older brain ages were associated with lower AD, RD, and TR values, but not with MWF or BPF values. This indicates that there are microstructural changes in the projections from the LC to the cortex in old age, but changes may not be due to myelin loss.

Conclusions: In conclusion, our anatomy based tractography methods allowed us to successfully generate LC tracts anatomically consistent with the CTT and detect age-related differences in microstructural features of this tract. Analysis of the local coil images is ongoing.

**STUDENT POSTER # 47**

**BEHAVIORAL AND METABOLIC PROFILES IN AN AGED, HUMANIZED APP/APOE MOUSE MODEL OF ALZHEIMER'S DISEASE RISK.** McLean JW, Bhattrai A, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.

Background: Research into Alzheimer's Disease (AD) pathomechanisms frequently utilizes animal models with dominant mutations; however, the vast majority (>95%) of AD cases are idiopathic. Animal models with AD risk factors represent an approach with potentially greater translational validity. The predominant genetic risk factor for AD is the Apolipoprotein E ε4 (APOE4) polymorphism, with APOE4 homozygosity conferring approximately 15-fold higher risk relative to the normative APOE3/3 genotype. Additionally, women are nearly twice as likely to develop AD. To address the translational validity of a risk factor model approach for AD research, we investigated behavioral and metabolic differences in a novel mouse model with homozygous expression of humanized (h) amyloid precursor protein (hAPP), encoding the precursor of the major protein in amyloid plaques, and replacement of murine APOE with humanized hAPOE3 or hAPOE4.

Methods: Aged (22-24 months) hAPP/APOE3 and hAPP/APOE4 mice underwent open field (OF), novel object recognition (NOR), EchoMRI body composition analysis, fasting blood glucose (FBG) and ketone body (FKB) determinations. Data were analyzed by 2-way ANOVA for effects of biological sex and APOE genotype followed by post-hoc t-tests and considered significant at $p<0.05$.

Results: Female mice traveled significantly farther and for a greater percentage of time during both OF and NOR, and interacted more with both familiar and novel objects during NOR. There were no group differences in either thigmotaxis or novelty recognition. EchoMRI body composition analysis revealed significant weight reduction in both male and female APP/APOE4 mice. While weight loss included a decline in both lean and adipose mass, greater loss of adipose tissue in APP/APOE4 mice resulted in lower body fat percentage and was the major contributor to weight loss.

Conclusions: Metabolically, female mice had lower FBG and higher FKB relative to males. The sex difference was greater in APP/APOE4 females, which had the lowest FBG and highest FKB. The hAPOE4-driven reduction in body weight, especially in adipose tissue, further indicates a metabolic consequence in mice expressing the AD risk gene. Collectively, this program of research contributes to the determination of the translational validity of the humanized APOE and APP mouse model for preclinical target identification and therapeutic development for AD.

**STUDENT POSTER # 48**

**NOVEL FINE MOTOR TASK FOR STUDYING KINEMATICS IN THE TGF344-AD RAT MODEL: APPLICATIONS OF NOVEL MACHINE LEARNING TECHNIQUES IN NEUROSCIENCE.**

Melick A, Lukacik D, Bimonte-Nelson H, Schaefer S, Beeman S, Verpeut JL. Arizona State University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is the most common form of dementia, with a projected 7 million individuals diagnosed in the United States alone by 2025 (Rajan et al., 2021). Early deficits in memory and executive function are difficult to distinguish from normal aging. Further, they are often observed at late stages of disease, reducing the use and efficacy of preventative options. New technologies aim to create more affordable and accessible alternatives to common techniques, including positron emission tomography (PET) scans. The Quick Behavioral Exam to Advance Neuropsychological Screening (qBEANS) task, a novel upper-extremity motor task accurately predicts functional decline over one year in MCI patients. Further, it predicts amyloid burden imaged with positron emission tomography with 88% sensitivity and bilateral hippocampal atrophy using structural MRI, suggesting it may reduce current diagnostic delays and disparities (Schaefer et al., 2020; Schaefer et al., 2022). To understand what neural components the qBEANS task is tuning into, we turned to a rodent Alzheimer's disease model, the Tg344-AD rat, and created a novel fine motor task to recapitulate similar aspects of the human task.

Methods: Female and male wildtype (n=12) and TgF344-AD (n=12) rats, a transgenic strain that expresses the amyloid precursor protein and presenilin 1 genes, were tested starting at 6 months of age when amyloid deposition and cognitive decline commences. First, animals were examined for fine motor ability (see methods at David Lukacik et al. 2024 poster). Reach kinematics, speed of retrieval, reach latency, and paw confirmation or position were analyzed using Social Leap Estimates Animal Poses (SLEAP), a machine learning software. Rodents were also tested in the Morris Water Maze (MWM) to examine cognition. Additional features of physical appearance and baseline motor function, including grip strength, were measured.

Results: First, we assessed whether the task could predict similar features as the qBEANS task. Pilot results demonstrate that rats learn to reach within 7 days. Total reaches per day were significantly different across bowl types ($p=.009$), with rats reaching more at latter stages (i.e. greater bowl difficulty), pointing to their ability to learn the task over subsequent training sessions. To ensure the task analogously modeled the self-perturbation of qBEANS, we analyzed the failure rate across bowl types to ensure difficulty was increasing. Bowl type significantly predicted reach failures ($p=.007$), with failures per day increasing from bowl 1 ($3.87 \pm 2.23$) to bowl 2 ($7.8 \pm 8.90$), and to bowl 3 ($11.2 \pm 5.95$), suggesting the task has increasingly difficult stages. Next, we assessed fine motor ability, cognition in the MWM, and grip strength. Grip strength was not significantly predicted by transgenic status at 6 months of age ($p=.366$). We expect to find decreased spatial performance in the MWM and impaired fine motor ability that decreases with age and increased amyloid deposition.

Conclusions: This work will create a comprehensive profile of the TGF344-AD rat model and characterize disease progression with an array of techniques, spanning from machine learning and behavioral measures to understand relationships between fine motor function and amyloid progression.

**STUDENT POSTER # 49**

**EXTENDED EXPOSURE TO ALZHEIMER'S RISK FACTORS INCREASES ALZHEIMER'S DIAGNOSIS RISK, AMPLIFIED IN APOE4 CARRIERS: IMPLICATION FOR DELAYED ONSET OF ALZHEIMER'S RISK FACTORS.** Merlini S, Vitali F, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.

Background: Obesity, diabetes, hypertension, hyperlipidemia, and depression are relevant Alzheimer's Disease (AD) modifiable risk factors (RFs). However, little is known about how the duration of these conditions, influenced by unmodifiable AD risk factors, such as chromosomal sex and APOE genotype, affects the associated risk. Modeling interactions between patient's temporal and clinical patterns, integrated with the probability of developing AD remains challenging, particularly when considering the multifactorial progression of AD. To address these challenges, we conducted a retrospective analysis using longitudinal data from the UK Biobank.

Methods: Inclusion criteria were age older than 55 years, no prior history of neurodegenerative disease, neurosurgery, or cancer, and enrollment with at least 3 years of follow-up. Propensity score matching was performed based on age at recruitment, educational level, center, and Charlson comorbidity index. Extended Cox proportional hazard models (CPHMs) for time-to-event prediction were used to evaluate the impact of the age-specific effect of multiple AD-RFs, in combination with sex and APOEε4 carrier status. Age stratification was evaluated when a violation of the hazard ratio (HR) proportionality assumption occurred during aging.

Results: Preliminary findings revealed RF-specific differences in AD on-set based on the age of RF diagnosis. After age stratification, the risk of developing AD was significantly greater than the APOEε4 effect if hypertension and diabetes were diagnosed before 62yo, while if diagnosed after 72yo, APOEε4 was the major contributor to increased AD risk. Obesity had a 54% increased risk of developing AD if diagnosed before 62yo and was associated with nearly 3 times increased risk if diagnosed between 62-72yo. Lastly, hyperlipidemia and depression were associated with an age-strata-independent increased AD risk of 33% and 69%, respectively.

Conclusions: This study identified critical tipping points indicating a decline in the hazard ratio of modifiable RFs with aging and a stronger association of APOEε4 with late-onset AD. Age stratification within CPHMs provided valuable insights into age-specific hazard ratios and identified age-dependent RFs. Furthermore, these results highlight interactions between age, sex, and APOE genotype which could inform a precision medicine approach for AD prevention.

**STUDENT POSTER # 50**

**NUCLEAR EXPORT OF TDP-43 IS FACILITATED BY ADAR2-MEDIATED RNA EDITING.**
Moore S, Julian D, Lorenzini I, McMillan M, Alsop E, Macklin-Isquierdo S, Lehmkuhl E, Kalab P, Hayes L, Zarnescu D, Van-Keuren Jensen K, Barmada S, Sattler R. Barrow Neurological Institute; University of Arizona, College of Medicine-Phoenix; University of Michigan; Translational Genomics Research Institute; University of Arizona; Johns Hopkins University, School of Medicine; Penn State, College of Medicine; Arizona Alzheimer's Consortium.

Background: TAR DNA binding protein – 43 (TDP-43) is a critical RNA binding protein involved in multiple steps of RNA processing, including transcription, splicing, RNA transport, stability, localization, and translation. TDP-43 is known to accumulate and form prion-like solid aggregates in the cytoplasm of cells. This behavior of TDP-43 has been well established as a pathological hallmark of a neurodegenerative disease spectrum encompassing amyotrophic lateral sclerosis and frontotemporal dementia (ALS/FTD) and has been described in Alzheimer's disease and related dementias. TDP-43 pathology has been hypothesized to contribute to disease pathogenesis through either nuclear depletion, leading to the loss of function, and/or cytoplasmic aggregation, leading to a toxic gain of function. Despite extensive research, mechanisms that initiate this pathology under disease conditions remain elusive.

Methods: Recent studies in our laboratory described aberrant adenosine-to-inosine (A-I) RNA editing in multiple brain regions of C9orf72 ALS/FTD, where we detected bidirectional changes of A-I editing. Since then, we have generated preliminary data suggesting that TDP-43 nuclear export can be regulated via Adenosine Deaminase Acting on double stranded RNA (ADAR)-mediated A-I RNA editing.

Results: We show that increased A-I RNA editing activity in mammalian cell lines induces TDP-43 translocation to the cytoplasm, mimicking what is observed in disease. In contrast, the presence of catalytically inactive ADAR2 or TDP- 43 carrying mutations within its RNA binding domains does not alter the nuclear localization of TDP-43. We further established that inosine-containing UI RNA oligomers can bind to TDP-43 in vitro, acting as a TDP-43 UG RNA binding motif mimic.

Conclusions: These findings demonstrate that aberrant increases in A-I editing induces TDP-43 nuclear export through an RNA-dependent mechanism.

## STUDENT POSTER # 51

**INCREASED GLUCOSE AND CA4 VOLUME INTERACT TO PROMOTE HIPPOCAMPAL MEMORY FUNCTION IN OLDER ADULTS.** Norman SL, Hoscheidt S, Matijevic S, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.

Background: Research suggests that glucose promotes hippocampal memory function and that the dentate gyrus (CA4) is particularly affected by glucose. Glucose regulation is gradually impaired with age and may contribute, at least in part, to normal cognitive decline. There may be factors; however, such as hippocampal volume, that mediate the effects of glucose on memory function. The present study examined the association between glucose and memory performance on a hippocampal-dependent memory task examining hippocampal subfield volume as a potential mediating factor.

Methods: Twenty-six cognitively asymptomatic older adults (mean age 68.9 ± 6.56 years, range=59-80 years, 73% female) underwent oral glucose tolerance testing (OGTT), neuropsychological testing, and magnetic resonance imaging (MRI). Blood glucose levels were obtained at fasting, one hour- and two hours- post glucose ingestion. Directly after glucose consumption, participants were administered the Rey Auditory Verbal Learning Test (AVLT).Structural MRI scans were used to calculate hippocampal volumes, including subfields, using FreeSurfer (version 7.3.2).

Results: Higher blood glucose levels relative to baseline (1hr post OGTT - fasting) were significantly associated with better memory performance on the delayed AVLT but only in individuals with larger volumes of the CA4 body. This relationship was also observed in the granular cell molecular layer of the dentate gyrus body. Findings were significant in the left, but not right, hippocampus. This relationship was not significant in other hippocampal subfields on either side.

Conclusions: Results further substantiate the critical role of glucose in hippocampal-dependent processes and suggest that increased glucose and volume of the left hippocampus, specifically the dentate gyrus and granular cell molecular layer, interact to promote hippocampal memory function. Findings provide evidence that glucose alone may not be sufficient to promote hippocampal-dependent memory, particularly in aging. The concomitant effect of glucose and structural integrity of the CA4 region may be an important factor in sustaining normal cognitive function.

**STUDENT POSTER # 52**

**CHOLINERGIC MUSCARINIC ANTAGONISM ON A SPATIAL MEMORY TASK: HYSTERECTOMY WITH OVARIAN CONSERVATION YIELDS COMPARABLE IMPAIRMENTS TO OVARIAN REMOVAL IN A RAT MENOPAUSE MODEL.** Oevermann MW, Lizik CR, Wu ES, Kelley-Wolfe K, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.

Background: Approximately half of women will experience gynecological surgery in their lifetime. By age 60, nearly one-third of US women will undergo hysterectomy, with the ovaries retained in about half of these cases. Surgical menopause includes variations in specific reproductive tract organ removal and retention. Two common surgical menopause procedures are bilateral oophorectomy, the surgical removal of both ovaries; and hysterectomy, the removal of the uterus. In women, bilateral oophorectomy, or hysterectomy alone, each increase dementia risk. Our laboratory developed a rat model of hysterectomy to broaden the understanding of surgical menopause variants that impact cognition. Using this model, we have discovered unique, persistent spatial working memory detriments resulting from hysterectomy with ovarian retention on a water radial-arm maze task with an increasing working memory load. Despite advances in alternative therapies for benign uterine conditions, hysterectomy remains the most common non-obstetrical gynecological surgical procedure. Thus, it is important to elucidate the drivers and parameters of neurobehavioral changes after hysterectomy. To yield further understanding of the neural mechanisms of the mnemonic effects after hysterectomy and other surgical variants, the current study investigated the impact of a pharmacological challenge with the cholinergic antagonist scopolamine. The importance of this experimental direction is underscored by the well-established literature that the cholinergic system shows changes during aging and with Alzheimer's disease, is intimately related to cognitive functioning, and that estrogens support cholinergic integrity.

Methods: Reproductively inexperienced Fischer-CDF rats from the NIA Colony were randomly assigned to the surgical treatment groups of Sham-control, Hysterectomy, or Ovariectomy (Ovx). Rats were then trained on the delayed-match-to-sample (DMS) plus maze, which included a series of information and retention trials, measuring spatial working memory and short-term retention. Next, rats were given a cholinergic muscarinic challenge via scopolamine administration and retested.

Results: Hysterectomized rats made more errors after scopolamine administration, with drug-induced detriments comparable to those seen in Ovx rats. Sham-control rats were not impacted by scopolamine treatment at the currently used dose. Therefore, a scopolamine dose subthreshold to intact animals effectively blunted spatial working memory in rats with the uterus or ovaries removed.

Conclusions: These results indicate that removal of the uterus yields a cognitive system especially sensitive to cholinergic muscarinic blockade, comparable to effects of bilateral ovarian removal. Given that the uterus has traditionally been considered an endocrine target, but otherwise dormant when independent of its communication with the ovaries, the collective data shift these considerations and indicate that the non-pregnant uterus influences non-reproductive functions, including cognitive processes and potentially associated brain circuits.

## STUDENT POSTER # 53

**CORTICAL BRAIN PERFUSION AND ITS RELATIONSHIP WITH HIPPOCAMPAL-BASED TASKS IN LONG-COVID**. Palmer J, Hoscheidt S, Rhodes, A, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.

Background: Changes to brain perfusion may be contributing to long-term cognitive dysfunction following COVID-19 infection. Both hospitalized and non-hospitalized cases demonstrate lower perfusion well beyond the acute phase of infection, however, it is unclear how the severity of respiratory symptoms relate to perfusion outcomes. Additionally, the hippocampus has been previously shown to be particularly sensitive to changes in blood supply. Therefore, the hippocampus may be vulnerable to perfusion changes from COVID-19, leading to pronounced long-term cognitive sequalae following infection. How the severity of respiratory symptoms and perfusion relate to cognitive performance using sensitive hippocampally-mediated tests has not been explored.

Methods: Seventy-eight participants completed a neuroimaging session and the Mnemonic Similarity Task and Face-Name Associative Memory Exam, tasks known to rely on the hippocampus. Participants were divided into four groups based on the severity of respiratory symptoms experienced during the acute infection: controls without COVID-19, those with COVID-19 and without respiratory symptoms, those with COVID-19 and reported respiratory symptoms, and hospitalized participants with respiratory symptoms from COVID-19. We used a pseudo-continuous arterial spin labelled (pCASL) pulse sequence to measure perfusion. We adapted a mask created by Liu et al. (2023) to assess total cortical perfusion in the gray and white matter, as well as perfusion within the three major arterial territories: ACA, MCA, and the PCA.

Results: The hospitalized group demonstrated lower total gray matter cortical perfusion compared to all groups (compared to controls $t(24)=1.88$, $p<0.05$; to those without respiratory symptoms, $t(32)=1.74$, $p<0.05$; and to those with respiratory symptoms, $t(32)=2.20$, $p<0.05$). White matter perfusion showed no differences between groups. A similar pattern was observed within each arterial territory. Out of all four memory measures, only pattern separation from the MST was related to gray matter perfusion, $r=.30$, $p<0.01$.

Conclusions: We found evidence for global perfusion dysfunction among hospitalized participants with severe respiratory symptoms over a year from COVID-19 infection. Additionally, there was a strong relationship between perfusion and pattern separation performance, suggesting that poorer perfusion may underpin some of the long-term COVID-19 cognitive symptoms.

## STUDENT POSTER # 54

**APOE4 INTERACTS WITH PERIMENOPAUSAL TRANSITION IN REGULATING CENTRAL AND PERIPHERAL LIPID METABOLISM**. Pan H, Mi Y, Qi G, Wang T, Brinton RD, Yin F. University of Arizona; Arizona Alzheimer's Consortium.

Background: Age, hormone depletion at menopause and the APOE-ε4 (ApoE4) genotype are among the top risk factors for developing late-onset Alzheimer's disease (AD). Findings from our and other groups have suggested that ApoE4 interacts with perimenopause in regulating a neuroimmune cascade encompassing mitochondrial dysfunction, metabolic reprogramming, and neuroinflammation. Our recent work revealed that astrocytes maintain brain lipid homeostasis by performing fatty acid (FA) degradation, and ApoE4 diminishes such capacity and thus promotes astrocytic lipid droplet (LD) accumulation. It is thus intriguing to determine whether lipid metabolism is involved in ApoE4-perimenopause modulation of the neuroimmune system and AD risk.

Methods: We first assessed mRNA levels of major metabolic processes in astrocytes acutely isolated from female humanized ApoE3 or ApoE4 mice before (6-month regular cycling), during (15-month irregular cycling), and post menopause (15-month acyclic). Body weight changes were measured, as well as circulating FA and leptin levels. Also, FA and mRNA levels in inguinal white adipose tissue (iWAT) were analyzed.

Results: Astrocyte gene expression analysis suggested a trend towards increase in fatty acid synthase (Fasn) levels upon perimenopause, which was sustained through menopause in ApoE4, but not ApoE3 mice. In contrast to the changes in Fasn, a key FA β-oxidation (FAO) gene carnitine palmitoyl transferase 1a (Cpt1a) was decreased in astrocytes from post-menopause mice regardless of ApoE genotype. Moreover, ApoE4- and menopause-induced metabolic reprogramming in the brain was coupled with peripheral metabolic changes. In line with changes in body weight, an elevation in circulating leptin levels and a trend towards increase in leptin mRNA levels in iWAT were found in ApoE4, but not ApoE3 mice upon perimenopause. Moreover, endocrine effect on plasma free FA levels was significant in ApoE4 mice only, whereas endocrine effect on iWAT free FA levels was significant in ApoE3 mice only. Analysis of key genes involved in FA metabolism also supported a lack of response of ApoE4 iWAT to endocrine transition.

Conclusions: Collectively, adaptations in lipid metabolism across the brain and periphery during female menopausal transition were disrupted by ApoE4, which could interactively contribute to a metabolic-inflammatory cascade that predispose ApoE4-carrying post-menopausal women to a substantially higher AD risk.

**STUDENT POSTER # 55**

**USING 3D ORGANOIDS TO INTERROGATE METABOLIC DYSREGULATION IN AGING & ALZHEIMER'S DISEASE.** Pennington T, Cerna S, Andrews M. Arizona State University; Arizona Alzheimer's Consortium.

Background: Aging is the primary risk factor for Alzheimer's disease (AD) and causes a progressive decline in function at the cell and molecular levels. Primary hallmarks of aging encompass dysfunctional mitochondria and nutrient-sensing pathways needed for stress adaptation and functional maintenance during metabolic strain. Impairments in these programs lead to bioenergetic imbalances and cell stress- both of which are implicated in the pathogenesis of AD. However, the mechanisms in which metabolic dysregulation elicits pathological changes in the brain and increases susceptibility to AD remains unknown- preventing the development of effective treatments. There is a need to understand the impact of age-associated metabolic changes in the brain and determine their role in neurodegeneration. This work utilizes 3D cortical organoids (hCOs) derived from human pluripotent stem cells (hPSCs) to characterize cell type-specific metabolic changes throughout aging and their role in neurodegeneration.

Methods: hCOs were differentiated until excitatory and inhibitory neurons and astrocytes (3 months) and aged phenotypes could be observed (5-7 months). In combination with cell type markers, immunostaining was used to analyze levels of tau phosphorylation, cell death, and astrocyte reactivity across 3-13 months. We then compared transcriptomic data from hCOs at time points before and after degenerative changes were detected to determine age-related gene expression changes associated with early degeneration. To obtain insight into disease-relevant processes associated with degenerative phenotypes, we performed single cell RNA sequencing (scRNA-seq) analysis using data from primary AD and control prefrontal cortex tissue. We then compared findings from aged hCOs with AD tissue to determine the correspondence of gene expression changes with in vivo disease. Conserved features will be targeted for follow-up studies to determine the mechanisms by which age-related metabolic changes contribute to AD.

Results: Immunostaining of long-term hCOs showed the ability to detect pathological tau phosphorylation and degeneration across neurons, along with increased astrocyte reactivity after 6 months. ScRNA-seq of hCOs from 3 and 6 months revealed differential expression associated with energy regulation and cell stress in neurons, and dysregulated insulin signaling and metabolic output in astrocytes. Transcriptomic analysis of primary tissue identified disease-specific gene expression changes in astrocytes and neurons and showed strong functional overlap with aged hCOs. Disease features conserved in hCOs include altered energy-sensing pathways, metabolic signaling, glucose utilization, and mitochondrial dysfunction.

Conclusions: Using long-term cultures of hCOs, we've established a platform to characterize age-related changes in metabolism and identify features of early neurodegeneration in vitro. We have identified cell-type-specific changes in metabolic programs associated with degenerative phenotypes both in vitro and in AD patient tissue. Gene expression changes indicate impaired energy metabolism and metabolic support from astrocytes, along with altered metabolic regulatory programs in neurons. Future work will utilize metabolomics-based approaches to investigate the functional impact of AD-related molecular alterations and determine the link between dysregulated metabolism and disease pathogenesis.

## STUDENT POSTER # 56

**IMPAIRED L-TYPE VOLTAGE-GATED CA2+ CHANNEL FUNCTION IN CEREBRAL ARTERIOLAR MYOCYTES FROM HUMANIZED APOƐ4 KNOCK-IN MICE.** Polk FD, DaSilva JF, Pires PW. University of Arizona; Arizona Alzheimer's Consortium.

Background: Cerebral small vessel disease (SVD) is associated with decreased cerebral blood flow (CBF) and impaired CBF autoregulation, contributing to 45% of dementia cases. Autoregulation is a physiological property of parenchymal arterioles that maintains brain perfusion constant even when facing large changes in blood pressure. In turn, loss of autoregulation can lead to intracerebral hemorrhages and vasogenic edema, which can cause dementia over time. Arteriolar autoregulation is intrinsically dependent on opening of L-type voltage-gated Ca2+ channels (CaV1.2) in vascular smooth muscle cells (VSMC), allowing for Ca2+ influx and vascular contractility. Despite observations that autoregulation is impaired in cerebral SVD, underlying mechanisms, as well as risk factors, remain poorly understood. Among various risk factors, the Ɛ4 allele of apolipoprotein E (ApoƐ4) is a significant genetic risk factor for cerebral SVD and is linked to impairments in cerebrovascular function, although whether this is due to loss of vascular contractility and autoregulation remains unknown. We hypothesized that ApoƐ4 allele expression leads to a reduction in Cav1.2 activity, thus impairing cerebral microvascular autoregulation and hemodynamic control.

Methods: Parenchymal arterioles isolated from 4-6 months-old male and female humanized ApoƐ4 knock-in (hApoƐ4-KI) and ApoƐ3 knock-in (hApoƐ3-KI) mice were used in this study. Using pressure myography, we assessed the contractile response of pressurized cerebral arterioles to 60 mM KCl-induced depolarization and CaV1.2 channel activation by FPL-64176 (300 nM). Additionally, we measured peak amplitude of nifedipine-sensitive currents in isolated arteriolar VSMCs using whole cell patch clamp electrophysiology to evaluate CaV1.2 channel activity.

Results: In male hApoƐ4-KI mice, we observed a diminished contractile response to receptor-independent VSMC depolarization in pressurized cerebral arterioles. Compared to hApoƐ3-KI controls, cerebral arterioles from male hApoƐ4-KI mice exhibit significantly reduced contractile response to FPL-64176. Whole-cell patch clamp recordings of step depolarization from -70mV to 50mV showed blunted CaV1.2 channel currents in isolated arteriolar myocytes from male hApoƐ4-KI mice. Conversely, no significant changes in contractile response to 60 mM KCl or FPL-64176 was observed between female hApoƐ4-KI and hApoƐ3-KI mice.

Conclusions: In summary, these finding highlight significant impairments in vascular function in male hApoƐ4-KI mice, particularly in response to VSMC depolarization and CaV1.2 channel activation in cerebral arterioles. These observations offer novel mechanistic insight into ApoƐ4-related alterations in vascular smooth muscle function, which may contribute to impaired regulation of CBF, potentially linking ApoƐ4 expression to the pathophysiology of vascular dysfunction in neurodegenerative diseases.

## STUDENT POSTER # 57

**NOVEL IMAGING SIGNATURES TO DETECT ROD MICROGLIA AFTER EXPERIMENTAL DIFFUSE TRAUMATIC BRAIN INJURY.** Pressman MM, Giordano KR, Griffiths DR, Hutchinson EB, Lifshitiz J. University of Arizona, College of Medicine-Phoenix; Phoenix VA Health Care System; University of Arizona; Arizona Alzheimer's Consortium.

Background: Inflammation and microglial activation are prominent in traumatic brain injury (TBI), both clinically and experimentally. Rod microglia, a variant of activated microglia, are observed abundantly in experimental diffuse TBI, particularly in the primary somatosensory cortex adjacent to areas of neuropathology. Their presence has also been noted in various neurodegenerative and neurological disorders such as Alzheimer's disease, epilepsy, stroke, and autism spectrum disorder. Currently, the detection of rod microglia relies on post-mortem immunohistochemistry (IHC) due to the lack of specific markers and the insensitivity of conventional in vivo imaging techniques like CT and MRI to microscale changes in microglia morphology.

Methods: Male and female rats weighing 262-384g received midline fluid percussion injury to induce diffuse TBI. Brain tissue was collected seven days post-injury and fixed for high-resolution ex vivo diffusion MRI microscopy, which included diffusion tensor imaging (DTI) and mean apparent propagator imaging (MAPI). These techniques aimed to detect subtle changes associated with rod microglia activation. The primary focus was on the primary somatosensory cortex, where rod microglia are known to accumulate. The imaging signatures indicative of increased restriction, particularly aligned with the long axis of rod microglia, were analyzed and compared with known rod microglia pathology via immunohistochemistry.

Results: The diffusion MRI microscopy techniques revealed a distinct imaging signature in the primary somatosensory cortex of injured brains. Specifically, there was increased diffusion restriction, particularly along the direction of the long axis of rod microglia. This abnormality in MRI corresponded spatially and quantitatively with the known distribution and density of rod microglia observed through immunohistochemistry (IHC). The findings suggest that diffusion MRI can potentially serve as a non-invasive method to detect rod microglia activation in vivo, which could have significant implications for understanding the histopathology and repair mechanisms in TBI and other neurological conditions.

Conclusions: This study demonstrates the feasibility of detecting rod microglia activation using diffusion MRI techniques after diffuse TBI in rats. The observed imaging signature of increased diffusion restriction aligns with the spatial distribution of rod microglia detected by immunohistochemistry. These findings highlight the potential of diffusion MRI as a tool for non-invasive detection and monitoring of microglial activation in vivo. Further validation and refinement of these imaging techniques could enhance our understanding of rod microglia's role in neuropathology, potentially aiding in diagnosis, prognosis, and therapeutic strategies for TBI and related disorders.

**STUDENT POSTER # 58**

**COMPARING OLDER ADULT STRESS LEVELS ASSOCIATED WITH COGNITIVE AND MOTOR TESTING TO ADVANCE EARLIER DEMENTIA SCREENING.** Reed AM, Chacon E, Schaefer SY. Arizona State University; Arizona Alzheimer's Consortium.

Background: Primary care physicians (PCPs) miss almost half of all Alzheimer's disease (AD) cases despite older adults seeing their PCP on an annual basis, with even lower rates of receiving routine cognitive testing during these visits. One reason for this lack of cognitive testing may be due to patient resistance because of the stress-inducing nature of cognitive testing, especially in older adults who are already experiencing cognitive decline. Thus, there is a clear need for an objective, brief, and patient-friendly screening tool in primary care to guide PCPs in referring patients for further neuropsychological evaluation. To address this need, we have developed an objective performance-based test that correlates with disease status and predicts the extent of AD progression over one year while also being associated with other AD biomarkers like brain amyloid and cortical atrophy. However, how stress-inducing our performance-based test is compared to a cognitive screen is unknown. Thus, the purpose of this ongoing study is to determine whether our performance-based test induces less test-related stress than a standardized cognitive test, which may lead to greater willingness to be tested.

Methods: To date, 15 participants across the cognitive-testing group (n=7; 4 females; 73.1±5.8 years) and the performance-based testing group (n=8; 5 females; 75.1±4.3 years) have been tested. The cognitive-testing group completed the Montreal Cognitive Assessment, while the performance-based testing group completed a functional upper extremity task that involved moving small objects (i.e., raw kidney beans) with a spoon in sequence with their nondominant hand. Each participant wore a wrist sensor to continuously monitor electrodermal activity (EDA) (16 Hz), enabling us to compare stress responses between groups. EDA signals were filtered and smoothed with a moving average window (window length = 16 samples), then separated into phasic and tonic components via continuous deconvolution analysis. Only the phasic components were analyzed here, where higher phasic activity indicated higher stress. The change in phasic EDA between test introduction (i.e., when the participant was told which test they would be taking) and immediate post-exposure were calculated, and an independent t-test was performed to compare the mean change between these time points between groups.

Results: Preliminary results indicate that the average change in electrodermal activity between test introduction and immediate post-exposure for the cognitive testing group (delta= 0.68 μS) was greater than the performance-based testing group (delta= 0.22 μS), but was not significant ($p>0.05$) at this time.

Conclusions: We acknowledge that these results are very preliminary, but they provide initial evidence that test-related stress is higher during traditional cognitive testing. We are underpowered, however, and more data are needed to test our hypotheses. Our long-term goal is to make AD screening more accessible by developing screening tools that may facilitate more widespread adoption.

**STUDENT POSTER # 59**

**THE RELATIONSHIP BETWEEN PATTERN SEPARATION AND OBJECT DISCRIMINATION.**

Rhodes A, Palmer J, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.

Background: Age-related declines in pattern separation are well documented to be related to changes within the DG/CA3 region of the hippocampus. The result is greater difficulty identifying highly similar objects from memory among older adults compared to younger adults. Additionally, studies of object discrimination find a similar pattern of results. These types of tasks display two stimuli simultaneously on the computer screen, removing the memory demand when identifying if the two stimuli are identical or different. Older adults have previously been shown to perform worse when the stimuli are highly similar with more overlapping features. However, the relationship between pattern separation and object discrimination has yet to be evaluated.

Methods: Data from a previous study in our lab were analyzed to correlate performance on the Mnemonic Similarity Task (MST) (Yassa & Stark, 2011) and a complex object discrimination task (Ryan et al., 2012). Ninety-one participants were included (average age = 58). The MST was completed in two phases, where the first phase had participants identify if common objects were found indoors or outdoors. In the second phase, participants identified if objects were old, similar, or new compared to objects seen in phase 1. The object discrimination task displayed two stimuli simultaneously on the computer screen, and participants indicated if they were identical or different. Stimuli were either squares or blobs and varied in degree of difficulty (easy or hard), resulting in four trial types differing on object shape and discrimination difficulty. Scores were calculated for object recognition and pattern separation on the MST and for correct discrimination on all four trial types on the object discrimination task. All measures were corrected for false alarms.

Results: Results indicated that pattern separation performance was positively correlated with object discrimination for hard blobs ($r=0.32$, $p<0.01$) and hard squares ($r=0.38$, $p<0.01$). Additionally, comparisons between younger (n=52) and older adults (n=39) indicated that older adults performed worse on pattern separation, $t(89)=4.78$, $p<0.01$, on hard blobs, $t(89)=2.42$, $p<0.05$, and on hard squares trials, $t(89)=4.20$, $p<0.01$.

Conclusions: We demonstrated that pattern separation and object discrimination are related. Potentially, age-related declines in pattern separation can be partially attributed to age-related declines in object discrimination. These results lay the groundwork for future research to more directly examine the specific functional changes underlying pattern separation and object discrimination declines in aging.

**STUDENT POSTER # 60**

**AN EXAMINATION OF AGE-RELATED DIFFERENCES IN AUTOBIOGRAPHICAL THINKING USING AN EXPERIENCE SAMPLING APPROACH: INSIGHTS FROM THE MIND WINDOW APP.** Puig Rivera VA, Cervantes LJ, Freveletti D, Andrews ES, Grilli MD, Andrews-Hanna JR. University of Arizona; Arizona Alzheimer's Consortium.

Background: The concept of healthy aging is slowly being redefined within the autobiographical thinking and memory literature, shifting from a perspective of natural deterioration towards one of adaptation. A novel approach that offers fruitful avenues for this research is experience sampling, as it allows for a closer look into adults' internal thought experience in real-world contexts. The Mind Window app is a smartphone application developed to gather repeated measures about the self-reported characteristics of participants' momentary thoughts via daily "check-in" questionnaires.

Methods: In this study, we used Mind Window to examine patterns of autobiographical thinking across the adult lifespan in a sample of 3,734 adults aged 18 - 89.

Results: Linear mixed effects analysis revealed findings that both supported and diverged from laboratory studies. In line with the observed Positivity Bias in healthy older adults (Carstensen & DeLiema, 2018), affective content of autobiographical thoughts was positively associated with age, such that older adults rated their autobiographical thoughts as containing more positive content compared to younger adults. Contrary to laboratory studies, however, episodic specificity was also positively associated with age, suggesting that older adults' autobiographical thoughts were more spatiotemporally specific than younger adults. Analysis of language use during a free response question following each check-in survey corroborated findings observed via self-report surveys. A closer examination also revealed age differences in the type of affective content that is more typical and persistent for each age group. Namely, younger adults described their typical and long-lasting thoughts as less positive in content, whereas older adults exhibited the opposite pattern, such that their more typical and long-lasting thoughts remained decidedly positive in content.

Conclusions: These findings offer insight into some of the everyday thought characteristics that may support psychological well-being in later life and hint at discrepancies between laboratory and real-world assessments of memory that deserve further study in future research in normal aging and Alzheimer's disease.

## STUDENT POSTER # 61

**THE IMPACT OF DEMENTIA AND THE LIVED EXPERIENCE OF COUPLES.** Santos B, Turner T. Midwestern University.

Background: This qualitative systematic review aims to understand the lived experience of persons living with dementia and their spouse. This is an area that has not been extensively researched. The primary objective of this systematic review is to understand the lived experience of couples living with dementia.

Methods: A review of the literature was completed focusing on the impact of dementia on the spousal relationship. Electronic databases, including EBSCOhost and Google Scholar, were searched with the following key terms used: “dementia and spouse psychosocial factors”, and “dementia and effect on couples”, and “dementia and effect on relationships”. Research studies included in this review utilized a qualitative research design. Data was collected from participants with a diagnosis of dementia and their spouse.

Results: This review included three qualitative studies. A total of 22 participants took part in semi-structured interviews. When synthesized, the researchers found the following five themes: Foundation of the Relationship, Intimacy for Connection, Changes in the Partnership Structures, Redefining Self, and Altruism and Positivity were consistent in helping maintain couplehood.

Conclusions: The influence of dementia on the spousal relationship is significant. When identified areas are addressed, the spousal relationship can provide strength throughout the disease process. From a clinical perspective, this study contributes insights into how health care providers and social services can more effectively address the needs of couples impacted by dementia.

## STUDENT POSTER # 62

**SEX-SPECIFIC HORMONE AND GENE EXPRESSION ALTERATIONS IN EXPERIMENTAL MODEL OF TRAUMATIC BRAIN INJURY**. Simmons A, Wilferd S, Pena V, Plaisier C, Bimonte-Nelson H, Sirianni R, Stabenfeldt S. Arizona State University; University of Massachusetts; Arizona Alzheimer's Consortium.

Background: Traumatic Brain Injury (TBI) results from a blow or jolt to the head and leads to complex pathologies that can extend years after the initial injury. Some of these pathologies such as blood-brain barrier (BBB) dysfunction and neuroinflammation contribute to chronic neurodegeneration. Unfortunately, current treatments for TBI focus on managing symptoms such as edema and intracranial hemorrhage rather than targeting the pathologies that lead to neurodegeneration. Additionally, little is known about how TBI pathology differs between sexes and how alterations in circulating sex steroid hormones contribute to chronic TBI pathologies. To address these challenges, our group employs both male and female models to assess sex-dependent pathologies of traumatic brain injury. In this project, our goal is to evaluate sex differences in circulating sex steroid hormones alterations, BBB disruption and neuroinflammation after TBI.

Methods: We used a well-established mouse controlled cortical impact (CCI) model to induce a moderate TBI over the primary somatosensory cortex in C57BL/6J mice. Male (n=10) and female (n=12) cohorts were injured at 9-10 weeks of age. Naïve cohorts served as baseline controls and injured cohorts were sacrificed at 24hrs and 72hrs post-CCI. Females began estrus cycle tracking via vaginal cytology 8 days prior to injury and continued until sacrifice. At the specified endpoint, animals were sacrificed to collect blood plasma and tissue samples. Plasma samples were analyzed with an LC-MS/MS hormone panel for testosterone, androstenedione, estradiol, estrone, progesterone, DHEA and corticosterone at the University of Wisconsin National Primate Research Center. Brain tissue was collected for immunohistochemistry (IHC) or RNA-sequencing analysis. For the RNA-sequencing, a 4 mm cortical punch was taken directly over the injury penumbra and contralateral hemisphere at sacrifice and samples were sent to Novogene Co for sequencing.

Results: Notably, we observe sex-specific alterations in circulating sex steroid hormones after TBI at both 24 and 72 hours. Females exhibit decreases in progesterone, androstenedione and testosterone at 24 and 72 hrs compared to naïve females, while males exhibit increases in DHEA and decreases in estradiol at 72 hrs compared to naïve males. Additionally, RNA-sequencing reveals the female 24 hr group exhibit 316 differentially expressed genes (DEGs) compared to all other injured groups. Furthermore, functional enrichment analysis of these DEGs shows the female 24-hour group had significant upregulation in genes associated with the following GO biological terms: regulation of neuroinflammatory process, innate immune response, and extracellular matrix disassembly.

Conclusions: Our results indicate there are sex-specific responses to traumatic brain injury, including sex specific alterations in steroid hormone profile and gene expression. Future analyses will focus on determining sex differences in BBB disruption through quantification of the expression of tight junction and adherens junction markers via IHC at the injury penumbra. Additionally, we aim to further elucidate sex differences in neuroinflammation by examining neutrophil extravasation and immune cell profile at the injury penumbra. This information will be critical for the improvement of TBI therapies that target neural regeneration and leverage biological sex as a variable.

## STUDENT POSTER # 63

**IDENTIFYING SYNAPTOME ABERRATIONS IN C9ORF72 ALS/FTD PATIENT-DERIVED CORTICAL NEURONS.** Spillman A, Bustos L, Hansen N, Garcia-Mansfield K, Gittings L, Alsop E, Van Keuren-Jensen K, Pirrotte P, Sattler R. Barrow Neurological Institute; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: An important aspect of neuronal function and communication in the central nervous system is the maintenance of synaptic networks, which is regulated via selective synaptic pruning. This process is aberrantly triggered in neurodegenerative diseases, including Alzheimer's Disease, Frontotemporal Dementia (FTD), and Amyotrophic Lateral Sclerosis (ALS). Glial cells are known to regulate and contribute to activity-dependent synapse remodeling with canonical "eat-me" and "don't eat-me" signals. As of today, it is still unknown whether synapse eliminations are initiated by activated glial cells or whether the diseased neuronal synapse has an altered protein composition that attracts glial cells for synaptic engulfment.

Methods: To test this hypothesis, we utilize a patient derived approach of age/sex matched induced pluripotent stem cells (iPSCs) differentiated into cortical neurons (CNs), in addition to postmortem autopsy tissue. To study proteins specific to the synapse, a series of centrifuge-based fractionations were performed to obtain a whole synaptosome (pre- and postsynaptic fractions) as well as an enriched postsynaptic density. Preliminary experiments include western blot characterization of iPSC-CN-derived synaptosomes, in addition to an unbiased proteomics profile of postmortem frontal cortex tissue-derived synaptosomes. To assess states of neuronal synaptic function, iPSC-CNs were cultured on a Microelectrode Array plate to assess metrics such as firing rate of action potentials, we well as network bursting and synchrony. Additionally, sister cultures of iPSC-CNs grown on coverslips were stained for synaptic markers to quantify synapse densities.

Results: The unbiased proteomics approach revealed an upregulation of metabotropic glutamate receptor 2 localized to the postsynaptic membrane, which is consistent with predicted cortical hyperexcitability. Interestingly, we also detected an upregulation of synaptic scaffolding proteins localized to both pre- and post-synapse, and a downregulation of members of the SNARE (Soluble N-ethylmaleimide-sensitive factor activating protein receptor) complex. The MEA data revealed that C9-FTD iPSC-CNs are hyperexcitable. Additionally, C9-FTD iPSC-CNs show more spontaneous and less synchronized network activity, indicating network destabilization and synaptic dysregulation. Microscopy analyses of synaptic connectivity and density are still ongoing.

Conclusions: Our work has shown synaptic aberrations across multiple levels of analysis, from structural and functional analyses Future work includes assessing the microglial contributions to synaptic dysfunction via "eat-me" and "don't eat-me" pathways.

**STUDENT POSTER # 64**

**INVESTIGATING AGE-RELATED CHANGES OF MPFC NEURAL RESPONSES TO VENTRAL HIPPOCAMPUS STIMULATION**. Srivathsa SV, Vishwanath A, Cowen SL, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

Background: Neural ensembles in the hippocampus (HC) and medial prefrontal cortex (mPFC) play a crucial role in spatial working memory, a process susceptible to decline during aging in mammals. These regions are connected via a monosynaptic, unidirectional projection from the CA1 layer of intermediate (iHC) and ventral (vHC) hippocampus to the mPFC (Jay and Witter, 1991, J. Com. Neurol. 313:574). Damage or inhibition to this connection leads to impairments in spatial working memory tasks. Performance on spatial working memory tasks is known to correlate with increased synchrony of hippocampal theta (8-12 Hz) rhythms to mPFC LFP and unit activity. However, little is understood about how monosynaptic iHC and vHC inputs engage mPFC neural activity along the dorso-ventral axis of the mPFC or how these change with age.

Methods: To investigate these questions, we delivered 25 individual biphasic electrical pulses ( halfwidth: 0.5 ms) ranging in amplitude from 100-600uA with a 30s interval between pulses across the CA1 layer in iHC and vHC of anesthetized male F344 young(10 months, n = 4) and old(24 months, n =4) rats. We simultaneously recorded evoked neural activity along the dorsoventral length of the mPFC using Neuropixels 2.0 probes. Recordings were obtained from all 4 shanks spanning 3.84 mm along the DV axis of the mPFC including the prelimbic(PL) and infralimbic(IL) regions (areas 24b and 25). Along the ML axis the shanks span 720 μm from layer II/III to layer VI.

Results: Upon stimulating either the iHC and vHC, we observed that increasing the stimulus amplitude resulted in a decrease in response latency and increase in the magnitude of the LFP response across the mPFC, with a larger relative increase in response to iHC stimulation compared with vHC. We also observed a layer-specific difference in evoked response amplitudes with relatively larger responses in the mPFC layers V/VI compared to layers II/III across all rats and stimulation conditions. Notably, the magnitude of LFP response in the IL regions of the mPFCwas larger than in the PL in young rats across stimulation conditions. In old rats, this increase in response magnitude in the IL region was not observed.

Conclusions: The LFP response magnitude to iHC/vHC stimulation also correlated with increased firing of mPFC neurons. The relative increase in the number of mPFC neurons activated by the stimulation was more in the IL region compared to the PL region in young rats, while in old rats, the similar response magnitude resulted in a similar number of neurons activated in both subregions . It appears that the vHC drive to the IL is greater than that to the PL in young rats and this difference does not emerge in old rats.

**STUDENT POSTER # 65**

**TAS2R38 SUPERTASTERS ARE ASSOCIATED WITH LOWER RISK OF ALZHEIMER'S DISEASE (AD) WITH THE ADVANCEMENT OF AGE.** Su CW, Chen K, Wang Q. Arizona State University; Arizona Alzheimer's Consortium.

Background: TAS2R38, or Taste Receptor 2 member 38 gene, is a member of the functional bitter taste receptors (TAS2Rs) which is responsible for the differential ability to taste bitter compounds. This receptor has also been reported to be expressed in many human tissues such as the brain, and implicated in innate immunity. Its association with Alzheimer's disease (AD) has yet to be investigated.

Methods: We investigated the relationship between the genotypes of common variants on the gene, and clinical measurements and biomarkers of AD of the subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI) project. The genotypes and longitudinal measures were retrieved together with other covariates (such as gender, education, and APOE4). We tested the association of the genotypes with cognitive assessments including CDR and MMSE, imaging biomarkers including structural MRI, PET amyloid and tau, fluid-based biomarkers including Abeta and ptau, and metabolic biomarkers including gut and lipid metabolites, by linear mixed effects (LME) modeling controlling for the above covariates. We also validated the findings using data from Parkinson's Progression Markers Initiative (PPMI).

Results: It was found that the presence of the supertaster haplotype is associated with a lower AD risk as age progresses. This association is seen in clinical cognitive assessments and brain imaging biomarkers, but not fluid-based biomarkers. For PPMI, significance was only found in subjects without Parkinson's disease.

Conclusions: TAS2R38 supertasters are associated with lower risk of Alzheimer's Disease with the advancement of age. In the future these findings will be further validated in additional AD cohorts and studies. The molecular mechanism behind the association will also be investigated.

## STUDENT POSTER # 66

**KNOWLEDGE OF RISK FACTORS FOR DEMENTIA AND ATTITUDES ON A DEMENTIA PREVENTION PROGRAM BY AGE AND ETHNICITY IN ARIZONA.** Talkad H, Chen Y, Bress A, Langbaum J, Tariot P, Pruzin J. University of Arizona, College of Medicine-Phoenix; Banner Alzheimer's Institute; University of Utah; Arizona Alzheimer's Consortium.

Background: Dementia disproportionately affects Hispanic communities, which may be partially attributable to disparities in resources to address modifiable risk factors. Addressing risk factors at younger ages would likely confer greater benefit than at older ages. Interest among Hispanic and younger persons participating in a dementia prevention program is unknown. We aimed to understand knowledge of dementia risk factors and attitudes toward prevention program participation among Arizona residents.

Methods: We surveyed southern Arizona residents aged ≥35 using an online self-administered questionnaire between July 13, 2021 and August 2, 2021. The survey asked about perspectives on risk of developing Alzheimer's disease and Alzheimer's disease-related dementias (AD/ADRD), knowledge of AD/ADRD risk factors, and attitudes toward cognitive health clinics and AD/ADRD prevention research. We examined the difference in responses between Hispanic and non-Hispanic White and younger and older respondents using chi-squared tests in SPSS.

Results: Overall, 30.7% of respondents were aware of any risk factors that increased risk for dementia with no differences between Hispanic and non-Hispanic White respondents. 76.4% of all respondents were "very" or "somewhat" interested in a dementia prevention program, interest was significantly higher in Hispanic (83.0% vs 73.3% "very" or "somewhat interested," $X2$ (3, N=1226) = 14.8, p=0.002) and younger respondents (82.2% vs 72.1% "very" or "somewhat interested $X2$ (1, N=1302) = 20.0, $p<0.001$).

Conclusions: General knowledge of risk factors for dementia is low, contrasting with high interest in a prevention program. Interest is higher in Hispanic and younger persons compared with older or non-Hispanic White persons. A dementia prevention program accessible to younger and Hispanic populations could help narrow dementia outcome disparities.

**STUDENT POSTER # 67**

**ADULTHOOD DIETARY CHOLINE SUPPLEMENTATION MODESTLY LOWERS METABOLIC SYMPTOMS RELATED TO ALZHEIMER'S DISEASE RISK IN THE TS65DN MODEL OF DOWN SYNDROME.** Tallino S, Etebari R, Leon H, Sepulveda I, Nath D, Bartholomew B, Velazquez R. Arizona State University; Arizona Alzheimer's Consortium.

Background: Down syndrome (DS) occurs in 1/700 live births and is the most common cause of early onset Alzheimer's disease (AD). Dietary choline intake has been proposed as a modifiable factor for AD and DS; choline is synthesized in the liver, but endogenous synthesis is not enough for the body's needs, with recommended intake set in 1998 to prevent hepatic steatosis. We have shown previously that AD mouse models with inadequate dietary choline have exacerbated AD pathology, and low circulating choline in humans correlates with high pathological AD burden. Perinatal choline supplementation (Ch+) studies have been performed in the Ts65Dn model of DS (Jackson Strain #005252), which protected offspring against AD-relevant pathologies such as loss of cholinergic basal forebrain (BF) neurons and decline in hippocampal-dependent cognition. To date, two studies showed that adulthood dietary Ch+ in AD mouse models ameliorates AD pathology and improves cognition; however, Ch+ in adult Ts65Dn mice has not been explored. Previously we found that adulthood Ch+ failed to reverse hippocampal-dependent cognitive outcomes in Ts65Dn mice, and did not affect age-dependent decline in circulating choline levels, though it modestly improved fasting glucose and lowered age-related weight gain.

Methods: Trisomic Ts65Dn mice and disomic littermate controls (n = 16-18 per diet per genotype, balanced by sex) were fed choline normal (ChN; 1.1 mg/kg) or Ch+ (5 mg/kg) diets starting at 4.5 months (mo), with behavioral testing at 13 mo and tissue collection at 14 mo.

Results: Here, we show that in a subset of trisomic females (n = 6-8 per diet), Ch+ modestly increased performance in a reverse place preference task via the automated IntelliCage behavioral phenotyping system, with no effect of Ch+ on other cognitive tasks such as attention, impulsivity, or conditioned avoidance. In additional subsets of animals (n=6-8 per sex, diet, and genotype) we further show that, while steatosis correlated with weight gain, Ch+ did not lower hepatic steatosis. We also found no difference between genotypes or diets in the intensity or colocalization of microglial activation markers in the hippocampus, and unbiased stereological analysis of BF cholinergic neurons (medial septum and vertical limb of the diagonal band) were unchanged by Ch+.

Conclusions: In conclusion, we reiterate that perinatal and/or early-life Ch+ is crucial in DS, as Ch+ in adulthood provides only minor metabolic benefits and fails to rescue neuropathological measures in the Ts65Dn mouse. Whether the DS population meets the recommended daily dietary choline intake has yet to be examined, and given that most Americans fail to reach adequate dietary levels in ways which may negatively affect metabolic parameters already dysregulated in DS, further investigation is warranted.

**STUDENT POSTER # 68**

**IDENTIFYING HIGH-RISK SUBGROUPS IN ALZHEIMER'S DISEASE PATIENTS: AN ANALYSIS OF DEEP EMBEDDED CLUSTERING IN WISCONSIN REGISTRY FOR ALZHEIMER'S PREVENTION PARTICIPANTS.** Tirambulo CVG, Merlini S, Paul M, Lizarraga C, Diaz-Brinton R, Vitali F. University of Arizona; Arizona Alzheimer's Consortium.

Background: Individuals in the early stages of Alzheimer's disease (AD) constitute a heterogeneous group, with diverse risk factor profiles such as chromosomal sex, apolipoprotein E (APOE) genotype, and comorbidities, evolving over distinct time courses. Within a prodromal phase that can extend for one to three decades, opportunities and challenges exist to identify crucial tipping points in its progression and opportunities for prevention.

Methods: Our study aimed to identify and characterize clusters of 389 high-risk AD patients (65.6±6.4 years old, 67.1% female, 38.8% APOE ε4 carriers), utilizing the Wisconsin Registry for Alzheimer's Prevention data from 2001 to 2022. We analyzed prospectively collected data covering patient characteristics (age, sex, race, and APOE ε4 carrier status), medical history (history of diabetes, hypertension, and hyperlipidemia), plasma biomarkers (amyloid-β (Aβ) 40, Aβ42, Aβ40/42 ratio, phosphorylated tau (p-tau) 181, and p-tau 217), and blood laboratory parameters (insulin, glucose, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol). Employing classical clustering methodologies (k-means (KMs), KMs with principal component analysis, hierarchical clustering (HC), and HC with dynamic time warping series) alongside a machine learning deep embedded clustering (DEC) algorithm, we compared outcomes. Contributions of different variables to the predicted cluster membership were assessed using SHapley Additive exPlanations values.

Results: Our DEC findings demonstrated promising results by: identifying more distinct risk profile patterns for each clusters (n=8) compared to classical methods (n=2); achieving a more evenly distributed partitioning of participants into clusters with increased stability as measured by Jaccard and entropy scores; and validating the clinical recognizability of clusters based on laboratory parameters, plasma biomarkers, physician consensus cognitive diagnoses, and Preclinical Alzheimer Cognitive Composite scores.

Conclusions: Going forward, outcomes from this initiative will enable a robust pipeline for integrating electronic medical record data, empowering the characterization of diverse patient populations, and achieving greater precision in treatment of the heterogeneous populations at risk for AD.

**STUDENT POSTER # 69**

**DIFFERENTIAL PREDICTION OF LEWY BODY PATHOLOGY BURDEN USING UNIVARIATE OR ML-BASED COMPOSITE NON-INVASIVE NEUROCOGNITIVE MEASURES.** Triebswetter C, Choudhury P, Zhang N, Ho A, Tremblay C, Belden C, Mehta S, Adler CH, Driver-Dunkley E, Shill H, Shprecher D, Serrano G, Beach T, Reiman E, Atri A, Chen K. University of Arizona, College of Medicine-Phoenix; Banner Sun Health Research Institute; Mayo Clinic, Arizona; Banner Alzheimer's Institute; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Lewy Body Dementia (LBD), categorized as either dementia with Lewy bodies (DLB) or Parkinson disease dementia, is the third most common type of dementia after AD and vascular dementia. The current gold standard for diagnosis of LBD is postmortem autopsy. We previously developed, using an artificial neural network (ANN) approach, a composite score based on standardized clinical, cognitive, and functional assessments to predict LBD pathology (Choudhury, et al, AAIC, 2024). In this study, we assess the performance of the ANN-based composite score prediction compared to the use of individual measures.

Methods: Participants included 145 deceased individuals selected from the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) at The Banner Sun Health Research Institute. Subjects were either diagnosed as cognitively normal or MCI at the time of their first clinical research examination. Each of 32 baseline clinical, cognitive, behavioral and functional measures was utilized as a potential predictor of LB pathology. Olfactory function was assessed using the University of Pennsylvania Smell Identification Test (UPSIT). Linear regressions assessed associations between demographic, clinical, cognitive, functional and behavioral measures and the postmortem measures of Lewy Body Disease.

Results: The strongest significant Pearson correlation between Lewy Body density and examined measures was observed for the UPSIT ($r=-0.64$ , p-value $<0.0001$). Other significant univariate predictors included Unified Parkinson's Disease Rating Scale II Total Off (UPDRSII, $r=0.38$, p-value $<0.0001$), Unified Parkinson's Disease Rating Scale III Total Off (UPDRSIII, $r=0.38$, p-value $<0.0001$), age ($r=-0.30$, p-value = 0.0002), and Trail Making Test B-A (TMTBA, $r=0.17$, p-value = 0.0445). We previously reported a stronger association of an ANN-based composite score with the same LBD measure ($r=0.86$, $p=2.47e-43$) when multiple measures were integrated, compared to the absolute correlation of UPSIT-LBD neuropathology density.

Conclusions: We found significant univariate relationships each for age and the cognitive and functional tests TMTBA, UPDRSIII, UPDRSII, and especially UPSIT with histopathological measures of LBD. Application of machine learning techniques, namely an ANN, using integration of several study measure formed a more powerful predictor of Lewy Body disease burden. Future studies with larger sample sizes will examine the generalizability of our analytic techniques for improved timely diagnosis and assessment of therapeutic efficacy in LBD.

## STUDENT POSTER # 70

**INTERPRETABLE DEEP LEARNING FRAMEWORK FOR UNDERSTANDING MOLECULAR CHANGES IN HUMAN BRAINS WITH ALZHEIMER'S DISEASE: IMPLICATIONS FOR MICROGLIA ACTIVATION AND SEX DIFFERENCES.** Trivedi MR, Joshi AM, Shah J, Readhead BP, Wilson MA, Su Y, Reiman EM, Wu T, Wang Q. Arizona State University; ASU-Mayo Center for Innovative Imaging; Latent AI, Inc., Princeton, NJ; Banner Alzheimer's Institute, Phoenix; Arizona Alzheimer's Consortium.

Background: The potential of Artificial Intelligence (AI) in investigating the genomic irregularities spanning various brain regions affected by Alzheimer's disease (AD) is yet to be fully explored. Specifically, region common and specific transcriptomic signatures that characterize AD-related cellular and molecular processes have not been thoroughly investigated. Applying AI to multi-omic data is also impeded by the lack of interpretability.

Methods: We applied an extensive deep-learning framework that consists of Multi-Layer Perceptron (MLP) to classify the AD vs controls using the bulk-RNA sequence data from three different brain regions in the Religious Orders Study/Memory and Aging Project (ROSMAP) from the RNAseq Harmonization Study of the AMP-AD consortium. We first trained MLP models to classify neuropathologically confirmed AD vs. controls for the three regions respectively. Utilizing predicted embeddings of the MLP, we modeled the distribution of expression profiles as a progressive disease trajectory in distinct brain regions. To enhance the interpretability of MLP models, we employed SHapley Additive exPlanations (SHAP) values and identified the most significantly AD-implicated genes, which serve as key nodes for subsequent gene co-expression network analysis.

Results: Our models exhibit robust performance in classification and prediction, and are validated by two external datasets: the Mayo RNA-seq (MAYO) cohort and the Mount Sinai Brain Bank (MSBB) cohort of AMP-AD. SHAP explainer revealed common and specific transcriptomic signatures from different brain regions. Their interpretations elucidated subtle molecular alterations in various brain regions, uncovering shared transcriptomic signatures activated in microglia and sex-specific modules in neurons relevant to AD. Notably, we identified, for the first time, a sex-linked transcription factor pair (ZFX/ZFY) associated with more pronounced neuronal loss in AD females, shedding light on a novel mechanism for sex dimorphism in AD.

Conclusions: In this study, we introduce an interpretable deep-learning framework for RNA-seq data from multiple postmortem brain regions of the ROSMAP cohort. We applied our trained models to transcriptomic data from two independent cohorts, demonstrating excellent predictive power in aligning transcriptomes with clinical and neuropathological traits. This highlights the framework's broader applicability in studying neurodegenerative diseases like AD.

**STUDENT POSTER # 71**

**AGING AND AUTISM: MODULATION OF THE CEREBELLAR NUCLEI DURING CRITICAL PERIODS OF DEVELOPMENT TO ASSESS SOCIAL CHANGES WITH AGE IN MICE.** Truong V, Lyle T, Verpeut J. Arizona State University; Arizona Alzheimer's Consortium.

Background: Autism Spectrum Disorder (ASD) is a heterogeneous condition dynamic to the aging process, yet little research focuses on the relationship between aging and ASD in regards to health outcomes. Social deficits, a hallmark symptom of ASD, limit essential healthcare engagement, which can vary between neurotypical and neurodivergent individuals as they age. However, it is unknown whether social deficits intensify or reduce with age in individuals with autism. One of the largest risk factors for the prognosis of ASD, besides genetics, is cerebellar injuries at birth (Wang et al., 2014), suggesting that the cerebellum plays a role in modulating certain aspects of social behavior. Specifically, inhibition of the cerebellar nuclei (CN) in rodents during critical periods of development results in decreased social behavior and decreased cognitive flexibility (De Bartolo et al., 2009; Tsai et al., 2018). The current study will target the cerebellar dentate nuclei (CN) to the ventral tegmental area (VTA) projection from the cerebellum, which is implicated in reward-driven pathways of social behavior involving dopaminergic neurons (Carta et al., 2019). Neurons within the CN are enlarged in children with ASD and abnormally reduced in older individuals with ASD (Mapelli et al., 2022). Thus, inhibiting the CN to VTA pathway during critical periods of development will be used to model social deficits observed in ASD.

Methods: To assess rates of social decline between non-ASD (n=16) and ASD phenotypes (n=16) with age, male rodents were perturbed with chemogenetic inhibition to the cerebellar nuclei (CN) to ventral tegmental area (VTA) pathway during developmental critical periods (Gi group). Neural pathways were inhibited with an inert ligand, clozapine-N-oxide (CNO), during postnatal days 21-35, followed by a 5-day washout period before behavioral testing. Behavioral tests, including the open field, 3-chamber social preference, olfactory habituation and dishabituation, and the Y-maze test, evaluated changes in behavior, which will be correlated with biological markers obtained from in-situ hybridization assays. Machine-learning pose-tracking software scored behavior between groups.

Results: Preliminary results show no significant differences in olfactory ability between untreated, CNO-control, and perturbed groups. Future analysis will ascertain the distance traveled, velocity, and time spent in regions of interest to classify behavior. This study anticipates ambulatory differences between juvenile and aged animals, such as decreased distance traveled and decreased average velocity in aged animals in the light and dark field task. We also expect Gi animals to have reduced sociability.

Conclusions: Comparing such results between manipulated and non-manipulated juveniles will indicate social behavior changes resulting from inhibition of the CN-CTA pathway, and the same comparison with middle-aged animals will indicate if these changes differ by age.

## STUDENT POSTER # 72

**ACTIVITY-DEPENDENT OVEREXPRESSION OF EGR1 IN THE HIPPOCAMPUS IMPROVES CONTEXTUAL MEMORY IN MICE.** Wallace SG, Higa N, Ho WH, Campbell JM, Okuno H, Gallitano AL. University of Arizona, College of Medicine-Phoenix; Kagoshima University; Arizona Alzheimer's Consortium.

Background: The immediate early gene (IEG) Early growth response 1 (Egr1) is expressed in neurons in response to neuronal activity and plays an essential role in encoding memory of the events that triggered its expression. Egr1 is activated by the neuronal stimulation that induces hippocampal long-term potentiation (LTP), a form of synaptic plasticity associated with memory formation. Mice lacking Egr1 have deficits in LTP and in long-term memory (after 24 hours). These findings suggest that increasing levels of Egr1 may improve memory. However, standard methods used to overexpress genes in the brain do not distinguish active versus inactive neurons. Failure to replicate the specific timing and location of Egr1 expression, and disruption of the unique pattern of activated neurons that form the memory engram.

Methods: To address this problem, we created an adeno-associated virus (AAV) expressing Egr1 under control of a promoter containing multiple copies of the synaptic activity response element (SARE) isolated from the IEG Arc (activity regulated cytoskeleton associated protein) to overexpress Egr1 in active neurons. Activity-responsive overexpression was validated in vivo by injection of AAV-ESARE-Egr1 into the hippocampal dentate gyrus (DG) and exposure of mice to environmental enrichment, electroconvulsive seizure, or home cage (control). Image J was used to quantify immunofluorescent (IF) labeling. Behavioral tests performed included the non-associative place recognition test, the open field test, and contextual fear conditioning.

Results: Quantification of IF levels and counts of fluorescently labeled cells showed that AAV-ESARE-Egr1 infusion into the mouse DG results in activity-inducible overexpression of Egr1 and increasing EGR1 IF in active hippocampal DG cells by 2.8 to 9.6-fold in response to neuronal activity. In the non-associative place recognition test, mice injected with control virus demonstrated recall 24 hours following an initial exposure to a novel context when Day 1 exposure times were 6 min. or 3 min., but not following a 1 min. exposure. In contrast, AAV-ESARE-Egr1 expressing mice displayed recognition following as little as a 1 min. exposure to the environment on Day 1. In the fear-conditioning test, injected mice displayed more freezing behavior than control virus injected mice.

Conclusions: We show that infusion of AAV-ESARE-Egr1 into the mouse DG results in activity-inducible overexpression of Egr1 in active hippocampal DG cells in response to neuronal stimulation. Injected mice show improved ability to recall a novel context and enhanced memory in contextual fear conditioning. These results suggest that increasing activity-dependent Egr1 expression in hippocampal DG cells enhances contextual memory in mice and suggest that developing molecules that upregulate Egr1 selectively in response to neuronal activity may have therapeutic use in disorders characterized by memory deficits or decline.

**STUDENT POSTER # 73**

**UNRAVELING SEX DIFFERENCES IN ALZHEIMER'S DISEASE SUSCEPTIBILITY: INSIGHTS FROM SINGLE NUCLEUS RNA-SEQUENCING IN RHESUS MACAQUES.** Watkins KL, Yang W, Bohlen MO, O'Day DR, O'Neill MB, Cayo Biobank Research Unit, Martínez MI, Starita LM, Montague MJ, Platt ML, Chiou KL, Shendure J, Snyder-Mackler N. Arizona State University; University of Washington; Duke University; Brotman Baty Institute; Caribbean Primate Research Center; University of Puerto Rico; University of Pennsylvania; Arizona Alzheimer's Consortium.

Background: Women make up almost two thirds of Alzheimer's Disease (AD) cases, but we still know relatively little about what underlies this disparity. One hypothesis suggests that sex differences in cell composition or function in the brain might predispose women to aging in a manner that increases their vulnerability to AD pathology. However, the challenge of obtaining human brain samples across different stages of life has hindered attempts to test this hypothesis.

Methods: To address this gap, we used single nucleus (sn)RNA-sequencing data generated from 5.3 million cells isolated from the brains of 55 (28 females) free-living rhesus macaques from Cayo Santiago, with the goal of identifying (i) normative age-associated and (ii) sex-associated differences in cell composition and gene expression. We sampled regions affected early in AD progression, including the midbrain, dorsolateral prefrontal cortex (dlPFC), anterior cingulate cortex (ACC), hippocampus, and entorhinal cortex (EC). We also sampled the mediodorsal thalamic nucleus (mdTN), lateral cerebellum, caudate, nucleus accumbens, inferior posterior parietal cortex (IPP), and primary motor cortex. The animals in this study range in age from 0.4 to 20.8 years, roughly equivalent to humans aged 1 to 63 years.

Results: Across all regions and samples, we identified 12 cell types, and here we report our preliminary results of sex and age difference in cell abundance at the broadest level, referred to as "cell class" (n=12 cell classes, e.g, basket cells, astrocytes, etc). In each region, we tested the effects of age and sex on the abundance of each cell class. On average, 55% of cell types differed in abundance in each region (N=33% in the hippocampus to 86% in the dlPFC; p adj <0.05). Astrocytes were most abundant in females, showing sex differences in the ACC, IPP, and mdTN. Microglia were significantly less abundant in females in both the EC and the mdTN. We found that 73% (11/15 cells across all regions) of the cell types with significant sex differences in abundance also showed significant differences in abundance with age, which is 50% more than expected by chance ($p<0.05$). However, we did not find any strong pattern of sex-biases recapitulating age effects: 64% of the cells associated with age and sex showed lower abundance in males and were less abundant in older animals.

Conclusions: While there may not be broad sex and age effects at the level of cell classes, it is possible that sex differences in AD risk are present at more granular levels. We are currently annotating heterogenous subtypes of cell classes and testing differential abundance at this increased level of resolution. The results of this ongoing work may uncover age and sex differences in abundance and transcriptional phenotypes that are not apparent at the broader cell class level.

**STUDENT POSTER # 74**

**EFFECT OF ESTROGEN AND PROGESTERONE LOSS ON NEUROGENESIS-RELATED SPATIAL LEARNING AND SEARCH STRATEGIES IN AGING FEMALE RATS.** Winter GM, Corenblum MJ, Pillutla, SV, Meredith J, Wene P, Menakuru N, Cowen SL, Madhavan L. University of Arizona; Arizona Alzheimer's Consortium.

Background: The adult mammalian brain contains active neural stem progenitor cells (NSPCs) that generate nerve cells throughout life, and neurogenesis is compromised with advancing age. Our previous work identified a specific critical period of decline in the neurogenic ability of NSPCs, (13-15 months) in aging F344 rats. These studies focused on male rats and included the characterization of deficits in different neurogenesis-relevant behaviors.

Methods: In the current study, we utilized different groups of aging F344 female rats (2, 6, 9, and 14 months old) to examine changes in cognitive flexibility, a correlate of the neurogenic function of hippocampal NSPCs present in the subgranular zone (SGZ) of the dentate gyrus, using Reversal Learning on the Morris Water Maze task (RMWM). To probe the role of the female sex hormones, 17b-estradiol (E2) and progesterone (P4), on aging NSPC function, a group of female rats also underwent ovariectomy (OVX) 2.5 weeks prior to experiments. Standard Morris Water Maze (MWM) learning for a fixed escape location was assessed over the initial 4 days of training followed by 2 days of training on the reversal version of the task where the platform was moved 180 degrees from the original location (RMWM). To support a fine-grained analysis of the search strategy employed by each animal, we utilized an automated system for strategy identification (Rtrack by Rupert Overall). This approach allows the identification of 9 unique search strategies during water maze performance. These strategies are classified into non-goal oriented, procedural, or allocentric search strategies.

Results: Preliminary analysis of our 2-month-old cohort (OVX n = 13, SHAM n = 11) looked at Corrected Integrated Path Length (CIPL), and Search Strategy. Two-way ANOVA using CIPL scores revealed no significant difference between groups in either the MWM ($p = 0.15$) or RMWM ($p = 0.78$). Further, we found no meaningful group-wise effect in Search Strategy during MWM or RMWM performance in 2-month-old rats.

Conclusions: These preliminary results indicate that estrogen and progesterone loss at young ages has no demonstrable effect on learning. Analysis of our 6-, 9-, and 14-month-old cohort data is ongoing and will also be presented.

## STUDENT POSTER # 75

**EXPLORING THE RELATIONSHIP BETWEEN EXTRACRANIAL CAROTID ARTERY DISEASE SEVERITY AND CHANGES IN BRAIN CORTICAL MORPHOLOGY**. Wiskoski H, Arias J, Zahra S, Khakwani K, Do L, Pugazhendhi A, Mushtaq R, Johnson K, Altbach M, Trouard T, Weinkauf C. University of Arizona; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Asymptomatic extracranial carotid artery disease (aECAD) is predominantly evaluated for stroke prevention but is increasingly recognized as a risk factor for Alzheimer's disease (AD). This study aims to understand whether ECAD is related to early structural brain changes relevant in AD pathology and cognitive dysfunction.

Methods: Whole-brain T1 and T2-weighted MRI data were processed using FreeSurfer to assess cortical morphology in 105 subjects, aged 55-85, with varying degrees of carotid stenosis. Default Mode Network (DMN) and AD Signature (ADS), regions important in neurodegeneration, were examined. Measures of cortical surface area (adjusted for total intracranial volume) and thickness were compared to carotid stenosis severity.

Results: A significant inverse relationship was observed between aECAD severity and ADS and DMN cortical volume. Analyzing these regions ipsilateral and contralateral to carotid stenosis displayed brain volume reduction is specific to the side of carotid stenosis. These changes were independent from age, sex, and cardiovascular comorbidities. In contrast to volume loss that is regularly associated with aging and dementia (decreased cortical thickness), we found that aECAD-related changes were driven by decreases in gray matter surface area.

Conclusions: Our study reveals that aECAD is associated with significant ipsilateral brain volume loss in the ADS and DMN brain regions, independent of age, sex, and cardiovascular comorbidities. A particularly intriguing finding was that these changes are driven by surface area loss, which is highly relevant in brain physiology but not commonly studied in ADRD research. Increased surface area is associated with higher IQ and is a key evolutionary change seen in humans more than other mammals. This type of brain change is not seen with normal aging and could represent a unique neurodegenerative pathway.

**STUDENT POSTER # 76**

**HIGH-RESOLUTION QUANTITATIVE T1 AND T2 MAPPING OF THE BRAIN TO ASSESS CHANGES RELATING TO EXTRACRANIAL CAROTID ARTERY DISEASE.** Wiskoski H, Johnson K, Arias J, Pugazhendhi A, Mushtaq R, Ahanonu E, Bilgin A, Trouard T, Weinkauf C, Altbach M. University of Arizona; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Asymptomatic extracranial carotid artery disease (aECAD) increases Alzheimer's disease and related dementias (ADRD) risk. Research has largely focused on using structural T1-weighted MRI to evaluate morphometric changes in the brain as early markers of disease progression. However, quantitative imaging techniques, such as T1 and T2 mapping, may better detect subtle cellular changes preceding atrophy and structural changes. This study employs two novel, high-resolution in-vivo techniques for T1 and T2 quantitative mapping of the whole brain to examine changes in participants with aECAD compared to age-matched healthy controls and healthy younger participants.

Methods: Two novel pulse sequences, RADTSE and IR-RADGRE, were adapted for use in in-vivo T1 and T2 mapping of the hippocampus at 3T. These acquisitions yield high-resolution (0.47 x 0.47 x 2mm) anatomical images and corresponding quantitative T1 or T2 maps with acquisition time totaling ~7 minutes per sequence. For 15 subjects (5 aECAD, 5 age-matched without aECAD, and 5 younger participants) conventional MPRAGE (1mm isotropic), high-resolution 2D T2-weighted (0.47 x 0.47 x 2mm) anatomical imaging, and T2 (RADTSE) and T1 (IR-RADGRE) quantitative mapping data were acquired of the brain. Using an iterative reconstruction algorithm developed in-house, RADTSE and IR-RADGRE data were processed to generate T1 and T2 quantitative maps for subsequent region-of-interest (ROI) analysis.

Results: Five regions of interest were assessed: the cornu ammonis 4 and dentate gyrus, cornu ammonis 1, cortical gray matter, parahippocampal white matter, and the corpus callosum. In white matter regions, it was found that the aECAD group had significantly higher T1 relaxation times than the age-matched control group. Additionally, T2 relaxation times were found to be significantly greater in the aECAD group than both the age-matched control and young control groups in regions of cortical gray matter and the corpus callosum.

Conclusions: The findings of this study reveal significant alterations in T1 and T2 relaxation times in both white and gray matter regions of subjects with aECAD. These changes provide new insights into subtle cellular alterations in the brain associated with aECAD, which could represent underlying pathology such as demyelination or neuroinflammation. This proof-of-concept work demonstrates the potential of high-resolution T1 and T2 mapping as an early biomarker of neurodegeneration. It remains to be seen whether these findings are more broadly relevant for ADRD risk assessment.

# Arizona Alzheimer's Consortium
# 25th Annual Scientific Conference

## Poster Presentation

## Abstracts

**POSTER # 77**

**INFLAMMATION, BRAIN AGING, AND DEMENTIA RISK AMONG FORAGER-FARMERS IN THE BOLIVIAN AMAZON.** Aronoff JE, Jenkins CL, Garcia AR, Buetow K, Beheim B, Rodriguez DE, Gutierrez RQ, Cuata JB, Chui H, Walters EE, Mack WJ, Gatz M, Finch CE, Irimia A, Law ME, Barisano G, Cummings DK, Hooper PL, Kraft TS, Stieglitz J, Gurven MD, Kaplan H, Trumble BC. Arizona State University; Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany; Universidad de San Simón, Cochabamba, Bolivia; Tsimane Health and Life History Project, San Borja, Beni, Bolivia; University of Southern California; Monash University, Melbourne, Victoria, Australia; Stanford University; Chapman University; University of Utah; Toulouse School of Economics, Toulouse, France; University of California Santa Barbara.

Background: Inflammation has been implicated in several chronic diseases in later life, including Alzheimer's Disease and Related Dementias (ADRD). However, studies of inflammation and health come primarily from post-industrialized populations (e.g., US, European). In these populations, inflammation is primarily caused by lifestyle factors like caloric excess and limited physical activity. Recent studies among a population of forager farmers in the Bolivian Amazon, called the Tsimane, have suggested a more complex relationship between inflammation and health. Despite their high inflammatory burden throughout life from constant pathogens and parasites, brain imaging and cognitive evaluations have suggested slower rates of brain aging and low prevalence of dementia compared to industrialized populations. However, while population comparisons are informative, they raise the question of whether this high infection-induced inflammation has any effect on brain aging.

Methods: We tested associations between a battery of measures of inflammation from blood samples and computed tomography measured brain volumes as well as diagnosis of mild cognitive impairment (MCI) or dementia (comparison: normal cognition vs. MCI/dementia). Our sample included Tsimane participants ages 39-94 years. Sample sizes were n = 472 for brain volumes and n = 219 for MCI/dementia status (7.5% diagnosed with MCI or dementia).

Results: Overall, we found little evidence that this high infection-related inflammatory burden was associated with brain volumes or cognitive disease risk.

Conclusions: Our results highlight the importance of assessing the different causes and types of inflammation for understanding its health risk. While lifestyle-related inflammation from caloric excess and limited physical activity can contribute to brain aging, high infection-related inflammation might not have a significant effect.

**POSTER # 78**

**BIOMARKER DISCOVERY IN ALZHEIMER'S AND NEURODEGENERATIVE DISEASES USING NUCLEIC ACID-LINKED IMMUNO-SANDWICH ASSAY.** Ashton NJ, Benedet AL, Di Molfetta G, Pola I, Anastasi F, Fernández-Lebrero A, Puig-Pijoan A, Keshavan A, Schott J, Tan K, Montoliu-Gaya L, Isaacson R, Bongianni M, Tolassi C, Cantoni V, Alberici A, Padovani A, Zanusso G, Pilotto A, Borroni B, Suárez-Calvet M, Blennow K, Hansson O, Zetterberg H. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Lund University, Lund, Sweden; Barcelonaβeta Brain Research Center (BBRC), Pasqual Maragall Foundation, Barcelona, Spain.

Background: Recent advancements in immunological methods accurately quantify biofluid biomarkers for identifying Alzheimer's pathology and neurodegeneration. Despite this progress, more biomarkers, ideally in blood, are needed for effective patient management and disease monitoring for Alzheimer's disease (AD) and other neurodegenerative proteinopathies.

Methods: We employed the Nucleic Acid-Linked Immuno-Sandwich Assay (NULISA™) central nervous system (CNS) panel for biomarker quantification in plasma, serum and cerebrospinal fluid (CSF) of patients with AD, mild cognitive impairment, Lewy body dementia, progranulin (GRN) mutation carriers and matched controls. We then looked at NULISA™ in the larger TRIAD and BioFINDER cohorts focusing on the development of tau pathology defined by tau [18F]-MK6240. LIMMA models evaluated the differential protein expression between groups adjusting for age and sex.

Results: NULISA™ identified p-tau217 and NfL as the most significantly deregulated plasma biomarkers in the AD continuum and GRN mutation carriers, respectively. Importantly, numerous novel and significant proteomic changes were observed in each disease comparison, which included proteins involved in synaptic processing, inflammation, microglial reactivity, TDP-43 and α-synuclein pathology. However, when contrasting tau pathology status amongst amyloid positive individuals, additional proteins were evidenced such as NPTX1 and NPTX2, NEFL, MAPT, IL6 and IL13. The WGCNA analysis identified one significant protein module that negatively correlated with group A-T- and positively correlated with A+T+ group, which set of proteins recapitulate findings from the initial LIMMA analysis.

Conclusions: We highlight the potential of next-generation biomarker identification tools, such as NULISA™, to detect novel proteomic features that incorporate established biomarkers like p-tau217 and NfL. Focusing on the development of tau pathology in the AD continuum proteins associated with tau pathology, inflammation, neurodegeneration and synaptic dysfunction were differentially expressed in the peripheral fluid.

**POSTER # 79**

**EVALUATION OF PLASMA PHOSPHO-TAU217 FOR ALZHEIMER'S DISEASE USING A FULLY AUTOMATED PLATFORM – AN INTERNATIONAL MULTI-CENTER STUDY IN PRIMARY AND SECONDARY CARE.** Palmqvist S, Anastasi F, Warmenhoven N, Tideman P, Mattsson-Carlgren N, Smith R, Ossenkoppele R, Tan K, Dittrich A, Skoog I, Janelidze S, Stomrud E, Zetterberg H, Kern S, Pilotto A, Quaresima V, Brugnoni D, Padovani A, Puig-Pijoan A, Fernández-Lebrero A, Contador J, Blennow K, Suárez-Calvet M, Hansson O, Ashton NJ. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Lund University, Lund, Sweden; Barcelonaβeta Brain Research Center (BBRC), Pasqual Maragall Foundation, Barcelona, Spain.

Background: Global implementation of blood tests for Alzheimer's disease (AD) would be greatly facilitated by access to easily scalable, cost-effective, and accurate tests. In this study, we evaluated a fully automated immunoassay for phospho-tau217 (p-tau217) using predefined biomarker cutoffs.

Methods: In this study, we evaluated a fully automated immunoassay for phospho-tau217 (p-tau217) using predefined biomarker cutoffs. The study included 1,767 participants with cognitive symptoms from secondary care of four independent cohorts in Malmö (Sweden, n=337), Gothenburg (Sweden, n=165), Barcelona, (Spain, n=487), and Brescia (Italy, n=230), and a primary care in Sweden (n=548). Plasma p-tau217 was measured using the commercially available Lumipulse immunoassay, with the main outcome being AD pathology determined by the cerebrospinal fluid Aβ42/p-tau181 ratio.

Results: Plasma p-tau217 detected AD pathology with AUCs ranging between 0.93 and 0.96. In secondary care, the accuracies ranged between 89-90%, the positive predictive values (PPV) between 92-95%, and the negative predictive values (NPV) between 77-86%. In primary care, the accuracy was 85%, the PPV was 82%, and the NPV was 88%. Using a two-cutoff approach, accuracies increased to 92-94% in secondary care with 12-17% in the intermediate group, and the accuracy in primary care was 92% with 16% in the intermediate group. No significant performance differences were observed between the Lumipulse immunoassay for p-tau217 and a high-performing mass spectrometry-based assay for %p-tau217 in secondary care, although %p-tau217 showed higher accuracy in primary care.

Conclusion: In conclusion, this fully automated blood test demonstrates high accuracy for identifying AD using predefined cutoffs. However, a two-cutoff approach might be necessary when used as a stand-alone test to confirm the presence of AD pathology, especially in primary care.

**POSTER # 80**

**IS DYSREGULATION OF MYELIN, OLIGODENDROCYTE OR NEUROFILAMENT CAUSING OR INFLUENCING WHITE MATTER RAREFACTION CHANGES?** Atri T, Pastrana González S, Lorenzini I, Intorcia AJ, Wermager Z, Walker JE, Qiji S, Shull A, Krupp A, McHattie R, Cline M, Borja C, Arce R, Aslam S, Mariner M, Beach TG, Serrano GE. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: White matter rarefaction (WMR) is a measure of overall white matter integrity and is usually defined by the degree of myelin loss, extent of tissue attenuation or vacuolization around small blood vessels, and density of reactive astrocytes (Alosco, et al 2019). For a long period WMR was considered to happen mainly as a result of vascular pathology, such as infarcts, hemorrhages and cerebral arteriolosclerosis. However, Santamaria Ortiz and J Knight PV in 1994 showed that this phenomenon is also present in Alzheimer's Disease cases without vascular disease. Beach et al. 2023 showed that AD pathology is a major contributor of this finding as well. They demonstrated that an increase of neurofibrillary tangles (NFT) correlates with higher WMR. To this date, the role oligodendrocytes play in cerebral WMR still remains elusive. For that reason, we aim to determine if NFT-WMR might be a result of axonal death, oligodendrocyte death or oligodendrocyte dysfunction that might result in myelin degradation.

Methods: Subjects included in this study were volunteers enrolled in AZSAND and the Brain and Body Donation Program (BBDP) at Banner Sun Health Research Institute. Subjects were chosen by searching the BBDP database. Control cases with different degrees of WMR, relatively low AD pathology and no infarcts were selected (n=39). Sections stained with H & E were used to determine WMR in each case. Immunohistochemistry was performed on 40 µm free floating sections and paraffin of the superior frontal gyrus to measure densities of: oligodendrocyte, myelin and axons. RNA was also isolated from white matter of the frontal cortex and qPCR was performed, targeting several genes related to oligodendrocyte injury. For image analysis, Image J was used to calculate area occupied by each marker. All statistical group analyses were done using Graph Pad Prism.

Results: In the image analysis of the immunohistochemical stains, there was a non-statistical increase of white matter stained by neurofilament in mild WMR cases (score of one) followed by a continued decrease of staining as WMR score increase. This data suggests axonal death in severe WMR. Oligodendrocytes were slightly reduced on mild WMR cases, while myelin showed a reduction in moderate and severe cases. In the qPCR results, Olig2 showed a slight increase in expression in the mild WMR followed by a significant decrease in severe WMR cases. There was a modest increase in expression of complement C4 and a modest decrease in expression of Tumor necrosis factor receptor 1 (TNFR1) in severe WMR cases compared to controls.

Conclusions: This data suggests that oligodendrocyte numbers seem to be very similar across different severity of WMR, while OLIG2 which is a transcription factor that activates the expression of myelin-associated genes in the oligodendrocyte-lineage cells, is reduced as well as myelin staining, suggesting that WMR might be partially due to oligodendrocyte dysfunction.

**POSTER # 81**

**SEX-SPECIFIC MOLECULAR PATHWAYS IN ALZHEIMER'S DISEASE: RESULTS FROM RNA SEQUENCING AND BIOINFORMATICS ANALYSIS.** Awong P, Walker J, Lorenzini I, Theng Beh S, Arce RA, Qiji SH, Intorcia AJ, Borja CI, Cline MP, Krupp AN, McHattie RD, Wermager ZR, Shull A, Mariner MR, Tremblay C, Beach TG, Aslam S, Serrano GE. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: There is growing evidence that women are disproportionately affected by Alzheimer's Disease (AD) compared to men. Studies indicate that when women develop AD the disease progresses more severely, they have higher levels of tau pathology, neuroinflammation, and synaptic dysfunction. These pathological differences suggest that the biological mechanisms underlying AD may vary significantly between men and women. Understanding these differences is crucial for developing effective treatments. In this study we examine sex-specific gene expression patterns using human brain bulk RNA sequencing to reveal molecular pathways and key genes involved in AD for each sex.

Methods: The cases were sourced from the Banner Sun Health Research Institute's Brain and Body Donation Program (BBDP) and included 114 subjects (57 controls and 57 AD patients), with 55 males and 59 females. Ribonucleic acid (RNA) was extracted from the human frontal cortex, sequenced, and analyzed, considering age and postmortem interval (PMI) as covariates Differentially expressed genes (DEGs) were identified through comparisons such as AD vs. control and various sex-specific contrasts. Pathway enrichment analysis identifies biological pathways that are differentially regulated, providing insights into the molecular mechanisms underlying AD. Cell-specific enrichment analysis determines the most affected cell types in AD for each sex, highlighting potential targets for intervention.

Results: AD females show more pronounced gene dysregulation with a higher number of up-regulated and down-regulated genes compared to males. v AD females exhibit more dysregulated genes in neurons, endothelial cells and oligodendrocytes, while males show more in microglia. Key pathways such as AMP-activated protein kinase (AMPK), forkhead box O3a protein (FoxO), and mammalian target of rapamycin (mTOR) signaling show sex-specific differences.

Conclusions: These data suggest sex-specific differences in the regulation of metabolism, cell death and signaling pathways. v These findings highlight the importance of considering gender in AD research and therapy development to create more effective, personalized treatment strategies.

**POSTER # 82**

**THE HUMAN RAP1 INCREASE GAMMA-SECRETASE ACTIVITY IN AN OXIDATIVE ENVIRONMENT.** Bae NS, Whetzel A, Lewis KA, 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. Deposition of amyloid β (Aβ) peptides in senile plaques is a hallmark of AD. γ-secretase produces Aβ peptides, mostly as the soluble Aβ40 with fewer insoluble Aβ42 peptides. Rare, early-onset AD (EOAD) occurs in individuals under 60 years of age. Most EOAD cases are due to unknown genetic causes, but a subset is due to mutations in the genes encoding the amyloid precursor protein that is processed into Aβ peptides or the presenilins (PS1 and PS2) that process APP. PS1 interacts with the epsilon isoform of glial fibrillary acidic protein (GFAPε), a protein found in the subventricular zone of the brain.

RAP1(TERF2IP) is a telomeric protein that is responsible for maintaining genome stability by preventing the ends from nuclear degradation and illegitimate fusions. RAP1 is a nuclear protein yet is also found in cytoplasm, though its role in cytoplasm is not well defined. Previously, our lab showed that RAP1 interacts with GFAPε in the cytoplasm alone and with PS1. GFAPε coprecipitates with RAP1 from human cell extracts. RAP1, GFAPε and PS1 all colocalize in human SH-SY5Y cells. Using a genetic model of the γ-secretase complex in Saccharomyces cerevisiae, we also demonstrated that RAP1 increased γ-secretase activity which was potentiated by GFAPε. Telomeres shorten with age, and correspondingly, the amounts of telomere protecting proteins decrease as cells replicate more. Oxidative stress is a major contributing factor of accelerated telomere shortening, and it also impacts the progression of AD. Here, we investigate the role of RAP1 in oxidative stress with respect to generation of Aβ peptide production.

Methods: Human U251 glioblastoma cells were grown and serum-starved for 48 hours. RAP1 levels were measured via immunoblotting, and Aβ peptides levels were measured in the media by enzyme-linked immunosorbent assays (ELISAs). The extent of oxidative stress on the cells was measured using CellRox detection kit.

Results: In this study, we showed that overexpression of RAP1 leads to an increase in Aβ peptides with a greater increase in Aβ40 than Aβ42. When cells were under oxidative stress through serum deprivation, the levels of RAP1 increased, and the levels of Aβ40 increased as well. The levels of Aβ42 remained unaffected in these conditions.

Conclusions: Our data indicate that RAP1 plays a role in regulating γ-secretase under conditions of oxidative stress. RAP1 levels increased, resulting in increased γ-secretase cleavage activity on APP. Under these conditions, more Aβ40 was produced likely to combat the oxidative stress. Thus, RAP1 may play a role in protecting the brain from oxidative damage.

**POSTER # 83**

**IMPACT OF SENESCENCE ON MITOCHONDRIAL DYSFUNCTION IN ALZHEIMER'S DISEASE.** Beh ST, Gulmen M, Dunckley N, Arce R, Borja C, Intorcia A, Walker J, Cline M, Qiji S, Mariner M, Krupp A, McHattie R, Wermager Z, Shull A, Tremblay C, Aslam S, Lorenzini I, Lue LF, Beach T, Serrano G. Banner Sun Health Research Institute; Boston University.

Background: Alzheimer's Disease (AD) is a neurodegenerative disorder characterized by progressive cognitive decline. In AD brains, mitochondrial dysfunction plays an important role, leading to impaired mitophagy, oxidative stress, and disrupted energy metabolism, which exacerbate AD pathology. Senescent cells, which accumulate with age, can worsen AD pathology. However, the progression of mitochondrial changes during cellular senescence is unclear, highlighting the need to study mitochondrial dysfunction in aging cells. This study compares gene expression profiles of fibroblasts from AD subjects and non-demented controls (NDC) across early, mid, and late stages of cell senescence to understand mitochondrial dysfunction in aging cells.

Methods: Human scalp samples were collected through the Brain and Body Donation Program and processed for fibroblast isolation and banking. The study included 5 NDCs (no dementia, minimal AD pathology) and 5 AD cases (clinical dementia, end-stage AD pathology). The AD group had a mean age of 84.6 ± 5.22 years, and the NDC group had a mean age of 87.4 ± 12.22 years. Fibroblasts were cultured through passages 3 (P3), 9 (P9), and 15 (P15) to study cell senescence. RNA was isolated, and RT-qPCR was used to quantify gene expression related to mitochondrial dynamics, function, stress response, cell cycle regulation, senescence, and apoptosis. Relative fold changes in gene expression were calculated using the $2^{-\Delta\Delta Ct}$ method and normalized to reference genes. Statistical analysis was performed using two-way ANOVA and Tukey's post hoc test ($p \leq 0.05$) with GraphPad Prism 9.0.

Results: AD fibroblasts showed downregulation of MFN1 and OPA1 and upregulation of MFF and DNM1L, indicating disrupted mitochondrial fusion and fission that worsen in later passages. Upregulation of TOMM40 and downregulation of TFAM and PPARGC1A suggest compromised protein import, biogenesis, and mitochondrial DNA maintenance, evident early in senescence. Impaired oxidative stress responses and defective mitochondrial clearance were indicated by the downregulation of SOD1, PARK2, and PARK7, with more severe effects in later passages. Upregulation of CDKN1A (p21) and CDKN1B (p27) signals enhanced cell cycle arrest and senescence, with increased expression in later passages, suggesting that more senescent cells contribute to AD pathology. Upregulation of BBC3 indicates increased pro-apoptotic signaling.

Conclusions: This study highlights significant disruptions in gene expression related to mitochondrial dynamics, function, and stress response in senescent fibroblasts from AD compared to NDC. These findings offer insights into developing therapies to mitigate mitochondrial dysfunction and senescence, potentially slowing AD progression.

**POSTER # 84**

**ASSESSMENT OF MICROSTRUCTURAL CHANGES IN WHITE MATTER HYPERINTENSITIES IN AGING AND MILD COGNITIVE IMPAIRMENT REVEALED BY ADVANCED DIFFUSION MRI.** Bergamino M, Nelson MR, Keeling E, Stokes AM. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: White matter hyperintensities (WMHs), which manifest as abnormal signals on T2-FLAIR MRI, are common in older adults. WMHs are linked to demyelination, axonal damage, gliosis, and higher dementia risk. This study used advanced diffusion MRI techniques to examine WMH microstructural changes in normal aging and mild cognitive impairment (MCI). Data from cognitively normal (CN) subjects and MCI patients were analyzed using free-water diffusion tensor imaging (FW-DTI), diffusion kurtosis imaging (DKI), and the mean signal DKI (MSDKI) models. Significant microstructural alterations in WMHs were identified, reflected by changes in FW-fractional anisotropy (FA), FW index (f), kurtosis metrics, and a correlation with MMSE scores.

Methods: Data was downloaded from the Alzheimer's Disease Neuroimaging Initiative (ADNI). The data included 55 cognitively normal (CN) subjects (39 females; mean age 76.1 years, SD 7.0) and 46 MCI individuals (16 females; mean age 74.2 years, SD 7.6). All participants underwent MMSE assessments and MRI scans at 3 Tesla (Siemens, Prisma) using MPRAGE, T2-FLAIR, and multi-shell diffusion MRI (dMRI) sequences. WMH volumes were segmented with the Lesion Segmentation Tool (LST version 3.0.0) in SPM12 (MATLAB v.2023b). Advanced dMRI techniques were applied: FW-FA and f from FW-DTI, mean kurtosis tensor (MKT) and kurtosis fractional anisotropy (KFA) from the DKI model, and mean signal diffusion (MSD) and mean signal kurtosis (MSK) from the MSDKI model. Differences in normalized WMH volume were assessed using a linear model with age and sex as covariates. Mean diffusion metrics were compared using linear mixed-effect modeling. Correlations between WMH volume and MMSE scores were assessed with Spearman's coefficients, while correlations of the diffusion metrics within WMHs and MMSE were analyzed using a linear model adjusted for age and sex.

Results: No significant age differences were found between groups ($t = -1.162$; $p = 0.248$), but MMSE scores differed significantly ($W = 1621$; $p = 0.003$). No significant differences in normalized WMH volume or dMRI metrics were found between CN and MCI groups in WMH or NAWM regions of interest (ROIs). Significant differences in all dMRI metrics between WMH and NAWM ROIs were observed within each group. WMHs had higher f, lower FW-FA, and lower DKI metrics compared to NAWM, as well as higher MSD and lower MSK. Higher t-values for all dMRI metrics were found in the CN group, compared to MCI. No significant correlations between CN and MCI groups were found for FW-DTI, MSDKI metrics, or for KFA and AK from DKI. There was a positive correlation between MKT, MK, and RK with MMSE scores, which was linked with lower kurtosis values and cognitive impairment. Finally, a weak correlation between WMH normalized volume and MMSE was found in the MCI group.

Conclusions: This study shows that WMHs exhibit altered microstructural characteristics compared to NAWM in both CN and MCI cohorts. These findings highlight the importance of considering WMHs when assessing dMRI biomarkers in populations at risk. Although no significant dMRI differences were observed between CN and MCI groups in WMH or NAWM regions, subtle vulnerabilities were noted in the NAWM of the MCI group. Advanced dMRI biomarkers can provide further insights into white matter changes related to aging and cognitive decline.

**POSTER # 85**

**A 3D CELL CULTURE AND INJURY MODEL TO STUDY NEURODEGENERATIVE EFFECTS DUE TO TRAUMATIC INJURIES.** Bjorklund G, Brafman D. Arizona State University; Arizona Alzheimer's Consortium.

Background: Almost 7 million individuals in the U.S. are living with Alzheimer's disease (AD) at a projected cost of almost $360 billion. While the majority of AD cases are considered sporadic, several studies have shown a strong relationship between traumatic brain injuries (TBI) and an increased risk of AD onset. To identify these possible mechanistic links, animal models have been extensively used in AD research and have largely confirmed the pathological findings in human postmortem tissue. However, it is questionable to what degree animal studies will translate to the human condition as animal models do not recapitulate all aspects of AD. Additionally, factors such as the complex and multi-cellular in vivo environment make it difficult to determine mechanistic links between TBI-induced cellular injury and AD-related phenotypes as well as resolve cell-autonomous versus non-autonomous aspects. To address the limitations of current animal-based models, we have developed an in vitro human cell-based model to study the biochemical, molecular, and cellular mechanisms that underlie TBI-induced AD.

Methods: Multipotent neural progenitor cells (NPCs) were generated from human induced pluripotent stem cells (hiPSC). NPCs were then differentiated to a cell co-culture consisting of neurons and astrocytes. The differentiated neurons and astrocytes were then mixed with 5% 85atrigel at 4.0e6 cells per ml. The cell/85atrigel mixture was then plated in suspended cell culture inserts to obtain a 14mm diameter by 2mm thick culture pellet. The culture pellet was then subjected to an injury using a custom-built electromagnetic compression device. Injury intensity to replicate mild, moderate, and severe TBIs, was modulated by varying the amount of compression of the culture pellets, e.g., 0.25mm compression for mild, 0.50mm for moderate, and 0.75mm for severe. Culture pellets were then subjected to several testing methods including a cytotoxicity assay, a live/dead cell assay, a membrane disruption assay, and a dendrite/axon measurement assay to confirm the cell injury process.

Results: Following cell injury, cytotoxicity was measured over 5 days by quantifying the release of lactate dehydrogenase into the culture medium. Results showed no significant differences between uninjured control cultures and injured cultures. Cell death was measured by calculating the ratio of Calcein-AM stained cells (live) and EthD-1 stained cells (dead) over a 5 day period post injury (DPI). Results again showed no significant differences between uninjured control cultures and injured cultures. Cell membrane disruption, a measure of injury and cell death, was then measured during and immediately following injury using calcein, a membrane impermeable dye, and EthD-1 a marker of cell death. Results showed a significant increase of membrane disruption with a 0.5mm compression load with no significant changes seen in cell death. Finally, neuronal dendrite and axon lengths were evaluated over 5 DPI to further determine injury effects. Significant differences were seen at 1 DPI with no significant differences at 3 and 5 DPI.

Conclusions: The results of this injury model evaluation indicates that a significant cellular injury is induced with no significant cell death when compared to uninjured control cultures. This in vitro model will help to eliminate the complexities associated with in vivo experiments by minimizing confounding variables and allowing a direct investigation of the effects of mechanical insult to hiPSC derived cell cultures.

**POSTER # 86**

**APOE, ABCA7, AND RASGEF1C ARE ASSOCIATED WITH EARLIER ONSET OF AMYLOID DEPOSITION FROM OVER 4000 HARMONIZED POSITRON EMISSION TOMOGRAPHY IMAGES.** Castellano T, Wang TC, Wu Y, Archer D, Janve V, Durant A, Regelson A, Cody K, Harrison T, Engelman C, Jagust W, Albert M, Johnson S, Resnick S, Sperling R, Bilgel M, Saykin A, Vardarajan B, Mayeux R, Alzheimer's Disease Neuroimaging Initiative, Betthauser T, Bennett DA, Schneider J, De Jager P, Menon V, Toson D, Mormino E, Dumitrescu L, Hohman T, Koran M. Vanderbilt University Medical Center; Stanford University; University of California, Berkeley; University of Wisconsin; Johns Hopkins University School of Medicine; University of Wisconsin School of Medicine; National Institute on Aging, National Institutes of Health; Massachusetts General Hospital; Brigham and Women's Hospital, Boston, Massachusetts; Indiana University; Columbia University Medical Center; The New York Presbyterian Hospital; Rush University Medical Center; Columbia University Irving Medical Center; University of California San Francisco; Mayo Clinic of Arizona.

Background: Genetics play a significant role in Alzheimer's Disease, but the genetics of the timing of when someone converts to amyloid positivity (the estimated amyloid positivity onset age (EAOA)) remains underexplored. Novel algorithms have shown that the rate of amyloid accumulation is uniform across large cohorts of research participants. Using this uniform rate of accumulation, we can then extrapolate when someone converted to amyloid positivity decades before their PET scans were acquired. We will use these algorithms to calculate EAOA from amyloid PET and then use EAOA in genetics studies to validate APOE associations and explore what genes beyond APOE effect the timing of amyloid onset. As the focus of my K76 aims, this work will be expanded to evaluate the genetics of EAOA in over 18,000+ Aβ PET from the Alzheimer's Disease Sequencing Project--Phenotype Harmonization Consortium.

Methods: Amyloid PET from 4,216 participants were harmonized and the SILA algorithm was utilized to calculate an individual's EAOA. EAOA was then used as an outcome variable in genome wide survival analyses. Gene and pathway analyses, tissue-specific gene expression, and genetic correlations with complex traits were also explored.

Results: APOE ε4 homozygotes converted to amyloid positivity five years earlier than ε3 homozygotes and ~1.5 years earlier than ε3ε4 heterozygotes. rs4147929, an expression quantitative trait loci (eQTL) for the AD-risk gene ABCA7 on chromosome 19 associated with earlier EAOA, with minor allele homozygotes converting to amyloid positivity four years before major allele homozygotes. The minor allele of ABCA7 was associated with increased expression of ABCA7, and increased expression of ABCA7 was associated with increased amyloid pathology in the brain in an independent autopsy dataset. Additionally, the risk-gene RASGEF1C was associated with an earlier EAOA.

Conclusions: Known AD-risk loci APOE, ABCA7, and RASGEF1C were associated with an earlier age of amyloid onset, with supporting evidence from tissue-specific gene expression analyses, offering insights into pathways targetable for intervention at the earliest stages of disease development.

**POSTER # 87**

**DEVELOPMENT OF A COMPOSITE SCORE TO PREDICT LEWY BODY PATHOLOGY BURDEN.** Choudhury P, Chen K, Zhang N, Tremblay C, Ho AH, Belden CM, Adler CH, Shill H, Mehta S, Driver-Dunckley E, Shprecher DR, Serrano GE, Beach TG, Reiman EM, Atri A. Banner Sun Health Research Institute; Arizona State University; University of Arizona; Banner Alzheimer's Institute; Mayo Clinic Arizona; Barrow Neurological Institute; Brigham and Women's Hospital; Harvard Medical School; Arizona Alzheimer's Consortium.

Background: Lewy body (LB) diseases can present with overlapping prodromal, cognitive, motor, autonomic or neuropsychiatric symptoms. Intuitively, greater symptom severity should correlate with greater pathological burden, but this has not been consistently shown. LB pathology does not translate to clinical expression in Incidental LB disease. While several composite scores/toolkits utilize overlapping schemes for diagnosis, a composite data-derived score to predict LB pathologic burden is lacking. We aimed to utilize an autopsy-confirmed cohort, and validated, brief, and standardized clinical, functional, pathologic assessments, and machine learning (ML)/quantitative modeling techniques to identify clusters and importance rankings among assessments/measures to predict LB pathologic severity and density.

Methods: A total of 234 subjects with neuropathological finding of LB at autopsy in the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) who were classified as Cognitively Unimpaired or Mild Cognitive Impairment after their first study clinical evaluation were included. Of these, 145 subjects had complete scores for 32 of 46 measures (clinical, cognitive, behavioral and functional) that were utilized as predictors of LB pathology. Olfactory function was assessed using the University of Pennsylvania Smell Identification Test (UPSIT). LB severity was assess by the Unified Staging System for Lewy Body Disorders (USSLB). Several ML algorithms and quantitative prediction models were explored and compared: artificial neural network (ANN), partial least square regression (PLSR), support vector regression (SVR), relevance vector regression (RVR) and ensemble forest regression (EFR) with leave-one-out (LOO) scheme. Game-theory based Shapley methods assessed the impact, including rankings, consistency and magnitude, of model predictors.

Results: RVR predicted aggregate LB density with large effect size ($R2 = 0.691$, $p < 0.00001$). ANN predicted USSLB severity stage with large effect size ($R2 = 0.74$, $p < 2.5e\text{-}43$). All other ML algorithms/models provided substantial prediction. Across all models, UPSIT was the most influential predictor (>65%), followed by Controlled Oral Word Association Test (COWAT) and age.

Conclusions: These preliminary and exploratory results support the utilization of ML techniques/models to assess LB pathologic burden with key measures collected in relatively small samples. UPSIT was consistently ranked highest impactful among clinical and functional measures/predictors. Integrated together in ML/data-derived composites, UPSIT, COWAT and other clinical characteristics may be of antemortem utility to predict USSLB stages.

**POSTER # 88**

**A MIXED-METHODS, DIGITAL HEALTH APPROACH TO SUPPORTING INDIVIDUALS WITH COGNITIVE IMPAIRMENT AND FAMILY MEMBERS IN RURAL COMMUNITIES: THE NORTHERN ARIZONA MEMORY STUDY.** Cerino ES, McCoy MC, Martinez M, Seaton TJ, Goldtooth AD, Livingston RA, Dopson R, Lucero L, McCarthy MJ. Northern Arizona University; Joe C. Montoya Community & Senior Center; Arizona Alzheimer's Consortium.

Background: The health and economic burdens of Alzheimer's disease (AD) are exacerbated for people living in rural social contexts who experience geographic barriers to care. There are currently few resources specifically designed to support socio-culturally diverse rural AD care dyads, including early detection of potential precursors to AD such as Mild Cognitive Impairment (MCI) and Subjective Cognitive Decline (SCD). The primary objective of the Northern Arizona Memory Study is to develop culturally informed and scalable resources to identify and support rural dyads at risk for AD. The purpose of this study is to introduce the NAZMS protocol and discuss its role in addressing dementia risk and promoting cognitive health in rural communities.

Methods: This dyadic study uses a mixed-methods, digital health approach. A sample of rural care dyads with cognitive impairment (SCD or MCI) is screened and recruited through partnerships with community centers across Northern Arizona. Consenting dyads complete separate semi-structured interviews where they answer questions about technology preferences for monitoring symptoms and engaging in remotely-delivered interventions. Next, care dyads complete separate baseline questionnaires assessing dyadic (e.g., experiences with caregiving/care-receiving) and health factors. Participants with cognitive impairment then complete a 14-day mobile protocol of brief end-of-day surveys and cognitive assessments delivered via study-provided smartphones.

Results: Data from the qualitative interviews provide dyad preferences for intervention development. Data from the quantitative protocol specify for whom (e.g., more caregiver support at baseline) and on which days (e.g., days when you feel more control over your stress during the mobile protocol) modifiable factors are related to better cognitive health in everyday life.

Conclusions: This study takes a mixed-methods, digital health approach to supporting rural care dyads at risk for AD by understanding intervention preferences and identifying the modifiable protective and risk factors that influence cognitive health in everyday life. The findings will directly support rural Arizonans and respond to national priorities in AD research for the development of community-based disease education programs and use of digital assessments of cognitive health and well-being.

**POSTER # 89**

**ACCOUNTING FOR WHITE MATTER UPTAKE IMPROVES BETWEEN TRACER AGREEMENT IN AMYLOID PET.** Chen Y, Protas H, Luo J, Li S, Esfahani MJS, Ghisays V, Lee W, Wu T, Reiman EM, Chen K. Banner Alzheimer's Institute; Arizona Alzheimer's Consortium; Arizona State University; University of Arizona; University of Arizona, College of Medicine-Phoenix.

Background: Amyloid PET allows in vivo measurement of amyloid neuritic plaque deposition in the brain. It is well recognized that the different amyloid PET tracers lead to different brain amyloid burden measurements. A Centiloid approach was proposed and widely accepted that defined a common amyloid burden scale and calibrated measurements from different tracers and quantitative pipelines. However, the level of agreement as measured by the strength of the correlation between the two measurements does not change. In this research, we test the hypothesis that the variability in amyloid measures from different tracers is partially caused by tracer-specific characteristics of white matter retention, and the between tracer agreement in amyloid burden measure can be improved by accounting for this variability.

Methods: F18 amyloid PET tracer calibration data from the Centiloid project (www.gaain.org/centiloid-project) was downloaded for all four F18 tracer-to-PiB pairs. The imaging data was processed using our standard in-house pipeline and generated mean cortical SUVR (MCSUVR) measurements of overall amyloid burden. Two approaches were examined to account for white matter contribution to the MCSUVR due to the inherent low spatial resolution of PET imaging: 1) a linear regression approach to regress out white matter signal using the SUVR of the FreeSurfer defined UnsegmentedWhiteMatter region as the regressor; and 2) a regional spread function (RSF) based partial volume correction (PVC) technique. Pearson's correlation coefficient was used to assess the agreement between F18 tracer-based measure and PIB. Steiger's test was used to determine whether accounting for white matter signal improves agreement.

Results: Accounting for white matter signal improves the agreement for all tracer pairs and both methods. For the regression based approach, the improvement was statistically significant for florbetapir ($p<0.001$) and flutemetamol ($p=0.03$) while do not reach significance for florbetaben and NAV4960. For the RSF PVC based approach the improvement was significant ($p<0.05$) for all four tracer pairs.

Conclusions: We demonstrated that between-tracer agreement of amyloid PET can be improved by accounting for white matter signal. Further investigation is ongoing to evaluate more sophisticated approaches to account for this signal and other potential confounds to the amyloid burden measurements.

**POSTER # 90**

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

Background: Reactive astrocytes have been implicated in the pathogenesis of C9orf72-FTD/ALS, the most common genetic form of this neurodegenerative disease spectrum. The astrocyte-secreted factor SPARCL1 - a key synaptogenic protein - has been shown to be pivotal to synapse maintenance and strength, yet no studies have carefully addressed whether SPARCL1 dysregulation may contribute to neurodegeneration. Interestingly, decreased SPARCL1 expression in CSF correlates with cognitive impairment in AD (Seddighi et al. JAD 2018, 61 401-414). Our study therefore aimed to ascertain whether similar SPARCL1 perturbations occur in C9orf72-FTD/ALS and how SPARCL1 dysfunction contributes to cortical neurodegeneration.

Methods: iPSCs from C9orf72-FTD/ALS patients (n = 3) and matched controls (n = 3) were differentiated into cortical astrocytes and subjected to bulk RNA-Seq and proteomics analyses. Postmortem frontal cortex tissues from C9orf72-FTD/ALS patients (n = 6) and non-neurological controls (n = 10) were analyzed using snRNA-Seq, with a focus on synaptic maintenance pathways.

Results: We observed a significant reduction of SPARCL1 protein in C9orf72-FTD/ALS patient-derived cortical astrocytes compared to controls ($\log2FC \approx -1.11$; $p = 0.009$). In the frontal cortex of C9orf72-FTD/ALS patients, astrocytic SPARCL1 mRNA levels were similarly diminished ($\log2FC \approx -0.33$; $p < 0.0001$). Furthermore, mRNA levels of several synaptic adhesion molecules, including neurexin and neuroligin family members, were notably decreased in excitatory neurons ($p < 0.0001$).

Conclusions: These data indicate that astrocytic SPARCL1 dysregulation is strongly associated with cortical synaptic dysfunction and neurodegeneration in C9orf72-FTD/ALS. Our ongoing experiments aim to characterize whether SPARCL1 loss directly impinges on synaptic maintenance, with a mechanistic focus on its presumed stabilization of neurexin/neuroligin interactions.

**POSTER # 91**

**TRANSCRIPTIONAL CHARACTERIZATION OF RELAXIN-3-POSITIVE NEURONS IN AGING AND ALZHEIMER'S DISEASE.** de Ávila C, Nolz J, Khatri D, Uzum Z, Intorcia A J, Chee S, Serrano GE, Beach TG, Gundlach AL, Mastroeni DF. Arizona State University; Regenerative Medicine Core; Arizona Alzheimer's Consortium; Banner Sun Health Research Institute; University of Melbourne.

Background: Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder worldwide and is characterized by clinical symptoms that include deficits in memory and cognition. There is an urgent need to better identify the neural networks that govern cognitive processes in humans and how they are impacted by AD pathology. The brainstem is a critical region that 'connects' the forebrain and the spinal cord and contains various nuclei involved in autonomic and complex functions (e.g., locus coeruleus) that are affected during the early stages of AD. In this regard, the brainstem contains the GABAergic nucleus incertus (NI), which has a demonstrated key role in rodents' contextual memory formation by directly inhibiting the hippocampus. Therefore, we mapped the human NI using the neuropeptide relaxin-3 (RLN3), a neurochemical marker primarily expressed in GABAergic neurons of the NI. In these novel studies, we investigated the transcriptomics of the RLN3-positive neurons in AD and controls. We also investigated potential RLN3 projections, from the NI to the hippocampus and cingulate cortex, in non-demented controls.

Methods: Using fresh-frozen postmortem human tissue provided by the Banner Brain and Body Donation Program, Sun City, Arizona, USA, we isolated RLN3-positive neurons from the NI of non-demented controls (N = 6), and subsequently from AD (N = 6) age/sex-matched subjects. After immunostaining, we will use laser-capture microdissection to isolate RLN3-positive neurons, followed by RNA sequencing and computational analysis. We used RNAscope in situ hybridization to investigate NI/RLN3 potential projections to the hippocampus and cingulate cortex.

Results: In AD, RLN3-positive neurons showed upregulation of genes including GNG4, CCDC17, MAGI2-AS3, and RBMS3. In addition, RLN3-immunoreactivity and RXFP3 mRNA colocalized in the hippocampus and cingulate cortex.

Conclusions: In AD, RLN3-positive neurons show upregulation of genes involved in inflammation, microtubule functioning, inhibition of cellular migration, and cell motility. Furthermore, the NI/RLN3 pathways potentially project to the hippocampus and cingulate cortex. Additional studies investigating RLN3 levels in pre- and early AD are required to understand the NI involvement in dementia.

**POSTER # 92**

**BRAIN BARRIERS BREAKDOWN IN ALS AND ALS-FTD.** Dominick M, Alsop E, Antone J, Van-Keuren Jensen K, Bowser R, Bakkar N. Barrow Neurological Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Neurovascular alterations have recently emerged as a common feature of many neurodegenerative diseases including ALS [1, 2]. These vascular alterations occur prior to motor neuron degeneration in a mouse model of ALS [3, 4]. Human postmortem studies of the blood-brain barrier (BBB) solidify these findings, with structural impairments of the neurovascular unit (NVU) affecting endothelial cells as well as supporting perivascular fibroblasts and pericytes [4, 5]. We have recently performed an extensive analysis of the human postmortem blood-CSF barrier (BCSFB) in ALS and non-neurodegenerative disease controls (NNDC) and discovered transcriptional and ultrastructural alterations in the NVU suggesting a leaky barrier into the central nervous system (CNS) [6]. In this study, we aimed to identify cell-specific changes in brain barriers as well as intrinsic differences in the BCSFB between slow progressing ALS (slow-ALS, disease duration <24months), fast progressing ALS (fast-ALS, disease duration >48months) and ALS with frontotemporal dementia (ALS-FTD).

Methods: We have performed single nuclear RNA-sequencing of postmortem choroid plexus tissues from slow-ALS, as well as global proteomic analysis of tissues from these same cases.

Results: We identified differential enrichment of various ALS related genes including Fus, C9orf72, hnRNAA1, and Ataxin2 in choroid plexus epithelial cells of ALS and ALS-FTD compared to NNDC. In addition, macrophages from fast-ALS but not slow- ALS BCSFB exhibit an enrichment in Th17 differentiation pathways highlighting the unique immune signature of various ALS subtypes.

Conclusions: This study highlights for the first time unique and intrinsic alterations in BCSFB cell types in ALS, and immune alterations specific to fast-ALS.

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**POSTER # 93**

**APOE STATUS IMPACTS RETINAL ARTERIOLAR FRACTAL DIMENSION IN INDIVIDUALS WITH NORMAL COGNITION.** Dumitrascu O, Badr A, Youssef A, Graff T, Andreev J, Saxena S, Vuong M, Li X, Caselli R, Wang Y, Woodruff B. Mayo Clinic Arizona; Arizona State University; Arizona Alzheimer's Consortium.

Background: Whereas the etiology of Alzheimer's disease (AD) is multifactorial, apolipoprotein E4 (APOE4) stands out as a well-established genetic risk factor. Given the urgent need for early detection and intervention strategies, there has been an increasing focus on identifying reliable biomarkers. A growing body of evidence is highlighting the role of vascular dysfunction in the development of AD. The retinal vasculature serves as a particularly promising venue for non-invasive assessment of central nervous system vascular health, and retinal fractal analysis (vascular branching, vessel tortuosity, and density) holds significant potential in AD classification. We aimed to explore if arterial and venous branching angles vary between APOE4 carriers and non-carriers with normal cognition.

Methods: We conducted a prospective case control study including cognitively intact subjects that underwent APOE testing and non-mydriatic color fundus photography. The digital retinal images were analyzed using retinal vessel tortuosity analysis script in MATLAB. We calculated retinal vascular branching angle for all retinal arteries and veins in a prespecified region of interest. We used generalized estimating equation (GEE) linear regression models to compare this vascular branching measures between the APOE4 carriers (homozygous and heterozygous) and non-carriers before and after adjusting for age, sex, and ethnicity.

Results: 41 APOE4 carriers (16 homozygous and 25 heterozygous) and 51 controls (APOE4 non-carriers) were enrolled. There were significantly less Hispanic or Latino among the APOE4 carriers compared with non-carriers (2.6% vs 20.8%, $p = 0.02$), but the 2 groups were matched for age and sex. Using GEE linear regression adjusted for age, sex, and ethnicity, APOE4 carriers had significantly narrower arterial branching angles compared to non-carriers ($B = -4.9$, 95% CI [-9.434, -0.368], $p = 0.034$). Particularly, APOE4 homozygotes had significantly narrower arterial branching angles ($B = -8.67$, 95% CI [-16.489, -0.851], $p = 0.03$), whereas heterozygotes did not show statistically significant differences ($B = -2.59$, 95% CI [-6.891, 1.713], $p = 0.238$). The venous branching angles showed no significant differences between carriers and non-carriers ($B = -2.286$, $p = 0.372$) for neither homozygous ($B = -5.79$, 95% CI [-12.742, 1.156], $p = 0.102$) nor heterozygous carriers ($B = 0.32$, 95% CI [-5.649, 6.291], $p = 0.916$).

Conclusions: Cognitively intact APOE4 homozygotes have significantly narrower arterial branching angles compared to non-carriers. Non-mydriatic retinal fundus photography in conjunction with vascular branching analysis might become a useful tool to screen for AD before cognitive symptoms manifest.

**POSTER # 94**

**PSEUDOTIME ANALYSIS IN ALZHEIMER'S DISEASE: IDENTIFYING KEY GENES OF MOLECULAR PROGRESSION IN THE BRAIN**. Ecca F, Song S, Naymik M, Huentelman MJ, Piras IS. Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Pseudotime (PT) methods are machine learning-based algorithms that extract latent temporal information from cross-sectional studies. These methods reveal progressive dynamic changes in gene expression underlying biological processes or diseases and offer new opportunities for drug design. This approach is particularly important for diseases such as Alzheimer's Disease (AD), where analyses are often limited to post-mortem tissues. We applied PT analysis to publicly available bulk tissue RNA-profiling data obtained from post-mortem brains.

Methods: We utilized data from the Accelerated Medicine Partnership-AD (AMP-AD) repository from eight brain regions: ACC, DLPFC, FP, IFG, PCC, PHG, STG, and TCX. Pseudotime trajectories were extracted using phenoPath, and their correlation with clinical and neurological variables was assessed. Enrichment Score Homogenate RNA Deconvolution (ESHRD) to estimate cell-type specific alterations through differential expression and pathway analysis as a function of disease pseudotime. Gene Ontology (GO) analysis and Multiscale Embedded Gene co-Expression Network Analysis (MEGENA) were employed to evaluate the enrichment pathways, modules, and key genes associated with pseudotime.

Results: We first extracted PT trajectories with the phenoPath method, investigating the correlation with clinical and neuropathological variables, including the Clinical Dementia Rating, Braak stage, disease status, and plaque density. We detected a significant correlation in 83.8% of the variable/pseudotime comparisons. We identified 866 genes significantly correlated with pseudotime, with concordant directions across all eight brain regions ($|r| >= 0.4$; Benjamini and Hochberg (BH) adj-$p < 0.05$). We observed consistent patterns at the cell-specific gene level across brain regions, with a significant increase in gene expression across PT for astrocytes, microglia, oligodendrocytes, endothelial cell genes, and a significant decrease for excitatory and inhibitory neurons. We conducted multi-brain coexpression network and key driver analysis across all datasets, identifying 358 significant key drivers, with 65 of them associated with PT in all 8 brain regions. Notably, 9 genes were significant key drivers in 7 distinct brain regions: CRYM, DRD1, GABRA4, KCNV1, LAMP5, PCP4, PCSK2, RASGRP1, and ZCCHC12. Interestingly, two of these genes have not previously been linked to AD.

Conclusions: In conclusion, our results highlighted key genes associated with AD, which might be useful targets for repurposed drugs or new molecule screening. Further in vitro and in vivo studies are warranted to validate the functional relevance of these genes.

**POSTER # 95**

**NEUROPSYCHOLOGICAL SUBTYPES IN HISPANIC NACC PARTICIPANTS.** Edmonds EC, Rapcsak SZ. Banner Alzheimer's Institute, Tucson, AZ; University of Arizona; Arizona Alzheimer's Consortium.

Background: Previous work has shown that subgroups of cognitively normal, subtle cognitive decline, and mild cognitive impairment can be identified by applying statistical clustering methods to neuropsychological data. With the National Alzheimer's Coordinating Center (NACC) dataset, empirically-derived neuropsychological subgroups were found to be predictive of progression to a diagnosis of dementia. A limitation of previous work is that participants are largely white and non-Hispanic, which limits generalizability of results. Thus, we aimed to examine the utility of these methods within a Hispanic sample.

Methods: Participants were 2,415 Hispanic NACC participants without a diagnosis of dementia (mean age=69.4 years, range 50-104; mean education=13.4 years, range 0-20). Raw scores on baseline neuropsychological measures were converted to z-scores based on performance of the sample, and cluster analysis was conducted using neuropsychological z-scores. Cluster groups were compared on demographics, vascular risk factors, and amyloid positivity using ANOVA and chi-square tests. Survival analyses examined progression to dementia across cluster groups.

Results: Five clusters were identified: (1) High-All (15.8%) with above-average performance in all cognitive domains examined; (2) High-Memory (19.6%) with above-average memory; (3) Low-Memory (20.0%) with an isolated weakness in memory; (4) Low-Attention (26.4%) with a weakness in attention; and (5) Low-All (18.2%) with multi-domain impairments. The Low-Attention and Low-All groups were older, had less education, and had higher rates of vascular risk factors (e.g., HTN, diabetes) relative to the two groups with above-average memory. The proportion of participants whose primary language was Spanish, and who completed testing in Spanish, generally increased across the cluster groups. Progression to dementia (n=190) differed significantly across clusters (High-All < High-Memory < Low-Memory = Low-Attention < Low-All), with no difference between the two groups with cognitive weaknesses. In a subset of the sample with biomarker data (n=235), the three groups with cognitive weaknesses or impairments showed higher rates of amyloid positivity relative to the High-All group.

Conclusions: Findings suggest that data-driven neuropsychological methods have utility for identifying nuanced cognitive subgroups and for predicting progression in a Hispanic sample. The Low-Attention and Low-All groups showed elevated rates of vascular risk factors and amyloid positivity, potentially reflecting mixed underlying pathology. The finding of higher rates of Spanish speakers in the more impaired groups may reflect lower access to education, disparities in health care, and other social determinants of health.

**POSTER # 96**

**WHAT'S IN A NAME? TERMS PERSONS SUPPORTING PEOPLE LIVING WITH MCI OR DEMENTIA USE TO DESCRIBE THEIR ROLE.** Erickson C, Clapp J, Gupta A, Kleid M, Harkins K, Stites SD, Peterson A, Karlawish J, Largent E. Banner Alzheimer's Institute; University of Pennsylvania; George Mason University.

Background: Best practice recommendations suggest a person close to a patient with mild cognitive impairment (MCI) or dementia be involved in their care. This person is often referred to as a "caregiver," though the term "care partner" has increasingly been used in research and care instead of "caregiver." Unlike "caregiver," "care partner" suggests a collaborative relationship between the patient and their support person, in which the patient actively participates rather than passively receives help. It is not known, however, what nomenclature people in this care role themselves use and why. Establishing terminology that accurately reflects the experiences of these individuals is important for research and care.

Methods: Semi-structured interviews were conducted with 14 people assisting patients with diagnoses of MCI or mild dementia, identified through an NIA-funded Alzheimer's Disease Research Center. Interviewees were asked if they identified as a caregiver, care partner, or something else. Data analysis was guided by a constructivist grounded theory approach and consisted of iterative rounds of coding with checks for intercoder reliability.

Results: Interviewees who provided relatively less assistance to patients, such as with activities of daily living (ADLs) and decision making, described themselves as a "care partner," while those providing relatively more saw themselves as "caregivers" or "caretakers." Preferred nomenclature may shift as the disease progresses and care needs change. Some interviewees currently preferring "care partner" suggested that "caregiver" was presently inappropriate because the patient was not yet that impaired. Support persons using "care partner" often highlighted the patient's dignity and agency and emphasized their shared responsibility for ensuring the patient's wellbeing. Finally, discussions of preferred nomenclature elicited reflections from the support person on how the patient's cognitive and functional impairments have changed the dyad's preexisting relationship (e.g., spousal, parental).

Conclusions: The terminology used to describe a person assisting in the care of a person with MCI or mild stage dementia has descriptive and normative dimensions. Asking support persons what label they use for themselves can provide insights into a patient's current care needs, social and functional qualities of the dyadic relationship, and demonstrate respect for the support person.

**POSTER # 97**

**TIME RESTRICTED EATING IN ALZHEIMER'S DISEASE (TREAD): A PILOT STUDY.** Geda YE, Krell-Roesch J, Zaniletti I, Chahal G, Smith T, DeCuna CJ, Aliskevich E, Gunning J, Khan N, Eagan D, Racette SB. Barrow Neurological Institute; Karlsruhe Institute of Technology, Karlsruhe, Germany; IZ Statistics LLC, Tampa, FL; Arizona State University; Arizona Alzheimer's Consortium.

Background: Time Restricted Eating (TRE), characterized by a restricted eating window and extended fasting periods, may impact cognition favorably via several potential mechanisms. 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 that include mitochondrial stress resistance, antioxidant defenses, autophagy, and DNA repair. The majority of studies of TRE focused on individuals with normal cognition. However, little is known about the impact of TRE on patients with mild cognitive impairment (MCI), an intermediate stage between normal cognition and dementia. Therefore, we are investigating the feasibility of implementing a TRE intervention among patients with MCI.

Methods: The study is conducted at Barrow Neurological Institute in the Division of Alzheimer's Disease and Memory Disorders in Phoenix, AZ. Funding is provided by Barrow Neurological Foundation. Eligible participants are aged 60-80 years, meet the Mayo Clinic Criteria for MCI, and have a body mass index >18.5 and <40.0 kg/m2. Additionally, participants must have a supportive family member or study partner to help facilitate study visits and intervention activities. The TRE intervention is 3 months and is characterized by 16 hours of fasting and an 8-hour eating window daily (16:8 regimen), on approximately 5 days/week. Participants meet with a registered dietitian to receive detailed instructions on how to follow a TRE regimen, learn about healthy dietary recommendations, and then meet weekly via phone to discuss progress, individualized strategies, and any challenges. Participants are asked to record their first and last calorie each day in a phone-based meal monitoring app that was designed for this study. Assessments are completed at baseline and after the 3-month intervention and include: 1) cognitive measures (working memory, executive domain, memory domain and global cognition); 2) psychological well-being and quality of life measures); 3) biomarkers of metabolic health (hemoglobin A1c, homeostasis model of insulin resistance); and 4) Alzheimer's disease biomarkers (pTau217, npTau217, pTau181, total Tau, Ab42/Ab40, pTau181/Ab42).

Results: By July 2024, we enrolled 7 participants (5 men, 2 women) with a median age of 68 years (range 66-82). Preliminary results from the 3 participants who completed the intervention thus far reveal that participants followed the TRE regimen on 93.3% of the recommended 5 days/week throughout the 3-month intervention. When considering all days throughout the intervention (7 days/week), the average eating window was 7.51 hours and participants consumed all of their calories within a 10-hour eating window on 92.7% of all days. All participants provided favorable feedback on their experiences, indicating that the 16-hour fasting window was not too long, that it was "very likely" that they could incorporate TRE into their life long-term, and that they benefitted from participating in the study.

Conclusions: The preliminary observation from the TREAD trial indicates that a TRE intervention among patients with MCI is feasible and well tolerated.

**POSTER # 98**

**IMPACT OF APOE4 DEMENTIA RISK AS A FUNCTION OF AGE IN UNDER-REPRESENTED GROUPS USING DATA FROM THE ALL OF US RESEARCH PROGRAM.** Ghisays V, Khajouei E, Piras IS, Goradia DG, Malek-Ahmadi MH, Chen Y, Naymik M, Saner D, Su Y, Huentelman MJ, Karnes JH, Reiman EM. Banner Alzheimer's Institute; University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Recent studies have raised the possibility that APOE4 has a smaller impact on the risk for Alzheimer's disease (AD) in non-Hispanic Black (NHB) and Hispanic than non-Hispanic White(NHW) individuals. Confirming that possibility in real-world cohorts could have major implications for research and care in under-represented groups(URGs). We used electronic health record(EHR) data from All of Us(AoU) to compare relative risk of a dementia diagnosis in these URGs and the impact of APOE4 carriage and allelic dose on dementia hazard.

Methods: We used EHR data from 9,784 Hispanic, 14,937 NHB and 60,388 NHW ages 60+ to characterize the risk of progressing to a diagnosis of probable dementia in combined APOE4 carriers, homozygotes(HM), heterozygotes(HT), and non-carriers(NC) using Cox hazards-ratio(HR) and 95%CIs. We used genomic data to extract genotypes and all ICD-9/10 codes related to dementia diagnosis or associated drug prescriptions to identify cases/controls. Effects of social determinant of health(SDoH) were explored with deprivation index.

Results: Results showed that APOE4 increased dementia diagnosis risk significantly in all groups and by allelic copy, but effects varied by race and ethnicity. In Hispanic, APOE4 carriers and HTs exhibited significant risk while HM differences were only marginally significant (Carriers:1.54, 1.25-1.91;HT:1.52, 1.22-1.89). In NHB, APOE4 carriers had a significant increased risk (Carriers: 1.25, 1.00-1.57), while we failed to detect differences in HM/HT. In NHW, risk increased significantly with APOE4 copy (HT:1.42,1.28-1.58; HM:3.70, 2.92-4.68; Carriers:1.55, 1.40-1.72). In Hispanic and NHB risk was higher than for NHW (Hispanic:2.44, 2.19-2.72; NHB:1.55, 1.38-1.75) and risk increased significantly with APOE4 copy number. Deprivation index indicated 5.8x higher risk of a diagnosis (Deprivation:5.75, 3.08-10.75).

Conclusions: Using diagnostic codes in 85,109 AoU participants, we observed trends to support APOE4 allelic dose effects overall and greater effects in NHWs as well as greater risk of dementia diagnosis with high deprivation and in URGs. This study illustrates the limitations of using a clinical diagnosis to characterize AD cases/controls in EHR datasets which can have biases and the potential value of using plasma pTau217 as an AD endophenotype to help overcome these and clarify the differential impact of APOE4 carriage and allelic dose in these URGs.

**POSTER # 99**

**VR AND SECONDARY FAMILY CAREGIVERS OF PEOPLE WITH ADRD: A SERIES OF FOCUS GROUPS ABOUT THEIR ROLE AND NEEDS- PRELIMINARY DATA.** Gómez-Morales A, Bahrami R. Arizona State University; Arizona Alzheimer's Consortium.

Background: Secondary caregivers of people with Alzheimer's disease and related dementias (ADRD) are family or friends who support the care provided by primary caregivers to their care recipients by assisting them different areas ranging from activities of daily living (e.g., bathing) to instrumental activities of daily living (e.g., managing finances) and emotional support. These individuals offer regular support in less intensive efforts; however, they also face some levels of stress, distress, and burden. This group receives little support and guidance regarding aiding the primary caregiver and their care recipient. Results are varied regarding how to support the caregiver and care recipient best and how to help them meet their needs; thus, more research needs to focus on understanding the needs and challenges of this crucial supportive population. This study aims to conduct a series of focus groups with family secondary caregivers to understand their needs better and create and tailor interventions to assist both primary and secondary family caregivers best.

Methods: This study consists of focus group interviews for secondary family caregivers of people with ADRD. The focus group consisted of a virtual 90-minute session with 5 to 9 participants. During the session, participants visualized a semi-immersive VR experience about Beatriz, an older Latina with Alzheimer's disease (AD), and participated in a discussion about AD, topics of interest to improve their caregiving skills, how to best support the primary caregiver and care recipient, and discussed an ideal intervention to cover their needs. Demographic data gathered during the screening and Zoom polls are analyzed using descriptive statistics. The group interviews are analyzed using qualitative thematic analysis.

Results: Two focus groups with 15 participants (N=15) have been carried out to this date. Initial conversations suggest that secondary family caregivers feel more empathetic and understand better memory loss and its effects on people. Managing challenging behavior and communication were the two most important topics for family secondary caregivers to learn. During the conversation, participants mentioned they feel more confident after the visualization of the VR as it provides a better understanding of what their loved one is going through and "how [the loved one] perceives things"; however, participants mentioned that the session felt scary as they never thought about the perceptions and thinking of a person with AD. Lastly, opinions were split on whether they wanted more interaction during the VR experience or preferred a "movie" type of immersive experience.

Conclusions: The conversation outcomes suggest that VR is a powerful tool for helping the participant see AD from a different perspective and gain empathy and confidence when supporting the primary caregiver and caring for their loved one with ADRD. The results will help create personalized training for secondary family caregivers and tailor the intervention "Through Alzheimer's Eyes."

**POSTER # 100**

**INVESTIGATING OPTIC NERVE ALTERATIONS IN PARKINSON'S DISEASE: A HISTOLOGICAL AND PROTEIN ANALYSIS STUDY.** Gonzalez A, Lorenzini I, Shull A, Qiji S, Walker JE, Theng Beh S, Arce RA, Intorcia AJ, Borja CI, Cline MP, Krupp AN, McHattie RD, Wermager ZR, Mariner MR, Aslam S, Tremblay C, Beach TG, Serrano GE. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Parkinson's disease (PD) is a neurodegenerative disease known by motor symptoms alterations that are caused by a loss of dopamine. PD patients have other non-motor symptoms usually present earlier in the disease progression such as hypotension, constipation, swallowing and vision difficulties. In addition, the main pathological protein aggregated in PD brains, phosphorylated alpha synuclein (α-syn), is also found in the retina and optic nerve (Beach, et al 2014; Cetin, et al 2014). Antemortem observations suggest that PD patients might have thicker optic nerves, which could result in an accessible, inexpensive diagnostic tool. In this study we measured the thickness of optic nerves of PD participants and investigated the level of different proteins that could explain possible nerve enlargement.

Methods: The initial step involved obtaining optic nerves collected at autopsy from 30 participants enrolled in the Brain and Body Donation Program (BBDP) program at Banner Sun Health Research Institute. Case selection included Alzheimer's disease (AD), PDs and controls. Optic nerve cross-sections were paraffin embedded and sectioned at 6 μm thickness. These sections were stained with hematoxylin and eosin (H&E), and immunostained for glial fibrillary acid protein (GFAP) to recognize astrocytes, neurofilament (NF) for axons, CNPase for oligodendrocytes (OL), and phosphorylated alpha synuclein (α-syn). Images were collected at 40X and 20X magnification to analyze H&E and immunostained sections, respectively. Image processing software "Image J" was used to measure the axon bundle circumference, diameter, dura thickness, and % of area occupied by each stained protein. GraphPad Software was used for group statistical analysis.

Results: While the optic nerve showed no significant changes in size across all groups, differences in the diameter of the dura layer of the PD group were noticed. There were no significant differences in the percentage area occupied by NF, GFAP, and OL between groups. However, a trend towards a decrease in GFAP expression was observed in the PD group, especially in PD males, suggesting a loss of the mechanical support that astrocytes provide. Forty percent of the PD cases included in the study presented α-syn inclusions in the dura layer.

Conclusions: Our data suggests that the dura layer surrounding the optic nerve may experience changes during PD progression.

**POSTER # 101**

**SYNAPTOSOME PROTEOMICS TO IDENTIFY MOLECULAR SIGNATURES IN DEMENTIA SPECTRUM DISORDERS.** Gopalakrishnan L, Sharma R, Martinez M, Bakkar N, Hansen N, Pirrotte P, Bowser R. Barrow Neurological Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Dementia includes a spectrum of neurodegenerative disorders, including Alzheimer's disease (AD), frontotemporal dementia (FTD), Parkinson's disease (PD) and Amyotrophic lateral sclerosis (ALS), all characterized by a progressive decline in cognitive function, which can include memory loss, and difficulty with thinking or decision-making. One of the main challenges is the heterogeneity of dementia subtypes, which makes it difficult to identify specific molecular targets that are relevant across all subtypes or those that may be specific to neurodegenerative disease. Synaptic dysfunction is a common feature in these diseases, with synaptic loss being a hallmark of neurodegeneration. This study aims to elucidate the proteomic changes in synaptosomes across different types of dementia by performing a quantitative proteomic profiling of synaptosomes isolated from the frontal cortex of AD, ALS, FTD, and non-neurologic control subjects.

Methods: Synaptosomes were isolated from the frontal cortex of age and gender-matched subjects diagnosed with AD, ALS, FTD, and non-neurologic controls. Synaptosomal proteins were collected and subjected to reduction, alkylation and trypsin digestion. The digested peptides were labeled with distinct TMT tags and checked for labeling efficiency and acquired on a Thermo Orbitrap Eclipse mass spectrometer.

Results: Using high-resolution liquid chromatography-tandem mass spectrometry coupled with TMT labeling, we identified a total of 8,212 proteins, of which 875 showed significant differential expression (ANOVA p-value < 0.05) across the dementia diseases. Key presynaptic proteins such as SNX9, SYNPR and postsynaptic proteins such as SYNPO and GRIN2A were identified, highlighting their roles in synaptic signaling and vesicle trafficking. Our analysis revealed distinct proteomic signatures for each dementia type, with significant proteins clustering differently across disease groups. Metabolic pathways were found to be altered in ALS, which exhibited distinct changes with the expression of proteins such as ALDH1A1, AIF1, and HBG1 showing significantly higher fold changes compared to AD and FTD.

Conclusions: Our findings underscore the potential of synaptosomal proteomics in identifying disease-specific molecular pathways and synaptic alterations in dementia. The differentially expressed proteins and enriched pathways, highlighted in ALS particularly those related to metabolic processes such as glycolysis, lipid metabolism, and amino acid metabolism, provide insights into the pathogenesis of these disorders. This study provides a comprehensive proteomic atlas of synaptosomes across dementia types and lays the groundwork for understanding of the molecular mechanisms underlying dementia.

**POSTER # 102**

**MINISCOPE IMAGING OF MICROGLIA BEFORE AND AFTER EXPERIMENTAL HEAD INJURY.** Griffiths DR, McQueen KA, Giordano KR, Lifshitz J. University of Arizona, College of Medicine-Phoenix; Phoenix VA Health Care System; Arizona Alzheimer's Consortium.

Background: Microglia are the most dynamic cell in the brain, constantly surveying their microenvironment. In response to brain injury, microglia rapidly react to the primary injury and then mediate the secondary injury cascade, defined by changes in cellular morphology. Despite their dynamic morphology, research has been limited to analysis of static, typically post-mortem images. In this study, we developed a novel approach for timelapse imaging of fluorescent cortical microglia in freely behaving transgenic mice. We hypothesize that closed head injury drives dynamic changes in microglia properties observed as increased microglia number and motility after injury.

Methods: Adult male CX3CR1-eGFP transgenic mice underwent surgery to secure miniscope hardware to the skull for time lapse imaging (30-60 images/hour). One week post-surgery, a miniscope was attached to acquire baseline images for one day. After baseline imaging, the miniscope was detached and replaced with a protective cap. Anesthetized mice received a weight drop head injury (Height: 94cm, Weight: 100g) that allowed free head rotation. After injury, the miniscope was reattached to timelapse image for one day.

Results: Qualitative results show increased microglia fluorescence, number of cells and cell motility over the 1 day time course post-injury.

Conclusions: Our study demonstrates that miniscope imaging, combined with closed head injury, has the potential to visualize and quantify dynamic microglia activity in the mouse brain in the acute post-injury period. Further studies are needed to investigate the relationship between injury parameters, long-term visualization of microglia activity, and behavioral function.

Funding: R21 NS131877, The Fraternal Order of Eagles, Arizona Alzheimer's Consortium

**POSTER # 103**

**SOCIAL NETWORKS AMONG CAREGIVERS OF PERSONS LIVING WITH DEMENTIA IN ARIZONA: FINDINGS FROM YEAR 1**. Guest MA, Peckham A, Sadow S, Schuchardt-Vogt C, Pittuch K, Hook J. Arizona State University; Arizona Alzheimer's Consortium.

Background: This study aims to understand the network compositions most effectively supporting the well-being and resilience of unpaid AD/ADRD caregivers and test the feasibility of spatial social network (SSN) data collection among dementia caregivers. Understanding network changes and benefits of older adults is significant in the context of aging and AD/ADRD, as these are times of unique and unfamiliar events, change, and adaptation. Understanding how social networks are used throughout the caregiving experience for ADRD caregivers is critical to identifying interventions that build supportive networks that promote well-being for ADRD caregivers.

Methods: We conducted an exploratory, cross-sectional, quantitative study with AD/ADRD caregivers using data collected via telephone surveys. Surveys included demographic questions and caregiver background. Outcome measures included the social support questionnaire, the reciprocal matters questionnaire, the Zarit Caregiver Burden scale, the Resilience Scale for Adults, and the life satisfaction scale.

Results: Our preliminary analysis involved running descriptives of our participant demographics and Pearson correlations to assess the association between social support and loneliness, burden, and resilience. We conducted an initial analysis of 73 individuals (75% white [13.7% Black/African-American], 84.9% female, and 38.4% being the spouse of the person they are providing care). Social network satisfaction was significantly negatively associated with caregiver burden (-.291 to -.334 with p-values between .022 and <.001) and loneliness (-.482 to -.661, p<.001), as well as positively associated with social well-being (.454-.747, p<.001), and resilience subscales of perception of self/future (.362-.425, p<.001 - .03) and social resources (.450-.544, p<.001) at the .01 level. At the .05 level, there was a significant positive association with the resilience subscale for family cohesion (.276 p=.025 for questions 1&3 at the .01 level and .437 p<.001 at the .05 level for question 2 on the Social Network Satisfaction Scale). Significant correlations at the .01 level (ranging between -.342 and -.661) between satisfaction with tangible, emotional, informational, and overall loneliness, indicating that higher social support is associated with lower loneliness. Additionally, higher levels of satisfaction with tangible, emotional, and overall social support are significantly associated with lower levels of caregiver burden at the .01 level. Interestingly, higher satisfaction with informational support is also significantly associated with lower burden at the .05 level.

Conclusions: Higher social network satisfaction is linked to lower caregiver burden and loneliness, as well as higher social well-being and resilience. The findings suggest that caregivers who are more satisfied with their social networks experience less caregiver burden and loneliness and report higher overall well-being and resilience. It is worthwhile to assess network compositions that are most likely to support caregiver resilience. In Year 2, we will implement a 15 to 30-minute interview to understand how caregivers perceive their networks to help or hinder overall well-being and change throughout their caregiving experience.

**POSTER # 104**

**CEREBRAL AND CAROTID ARTERIES FUNCTION IN MARFAN SYNDROME: EFFECTS OF EXERCISE TRAINING.** Gusek B, Priday C, Folk R, Vallejo-Elias J, Esfandiarei M. Midwestern University; University of Arizona.

Background: Marfan syndrome (MFS) is a connective tissue disorder caused by mutations in the fibrillin-1 (FBN1) gene. The mutation manifests in a variety of phenotypic changes in the musculoskeletal, cardiovascular, and pulmonary systems, with a notable vascular effect leading to aortic aneurysm, dissection, and rupture. In recent decades, better diagnostics and advances in medical and surgical treatments have increased the life expectancy in individuals with MFS, hence, other vascular complications have become more concerning. Aging is the dominant risk factor for clinically significant atherosclerotic lesion formation affecting most often the coronary and carotid arteries. Aneurysms of the extracranial carotid artery have been associated with MFS but are mostly caused by atherosclerosis. Studies have shown that carotid artery tortuosity is highly associated with connective tissue diseases, particularly MFS, Loeys-Dietz syndrome, and neurofibromatosis type 1.

There is also a connection between MFS and intracranial aneurysms (IA). The prevalence of IA in patients with aortic disease is quadrupled compared to that in the general population. There is a modestly increased prevalence of ischemic stroke in hospitalized patients with MFS when compared with healthy controls. The reduced cerebral blood flow triggered by cardiac and peripheral vascular dysfunction could further make the brain more vulnerable to vascular dementia and Alzheimer's pathology. Despite these reports our understanding of cerebrovascular and carotid artery function and structure in connective tissue disorders such as MFS is very limited.

The cardiovascular benefits of moderate exercise training have been well documented in the literature. In addition, studies have shown that aerobic exercise can improve cognitive function, decrease neuropsychiatric and neurodegenerative symptoms. In this study we aim to investigate the impact of MFS pathogenesis and mild aerobic exercise on other vessels such as the posterior cerebral artery and carotid artery.

Methods: At 6 weeks of age, male and female control (Fbn1+/+) and MFS (Fbn1C1041G/+) were divided into three experimental groups: Ctrl, MFS, MFS + exercise. MFS mice were subjected to an exercise regimen of 8m/min, 30min/day, 5days/week. At 7 months of age, in vivo ultrasound imaging was performed to measure the carotid artery pulse wave velocity (PWV), wall thickness and distensibility and the peak systolic velocity (PSV) of the posterior cerebral arteries.

Results: Our results showed that carotid artery PWV (an index of aortic stiffness) and wall thickness were significantly increased in MFS mice compared to Ctrl. Mild aerobic exercise significantly reduced both PWV and wall thickness of carotid artery in MFS mice. The carotid artery wall distensibility was significantly decreased in MFS mice compared to Ctrl, which was normalized to a healthy level in exercised MFS mice. The posterior cerebral artery PSV was significantly reduced in MFS mice compared to Ctrl and was completely normalized in response to mild exercise.

Conclusions: This study offers an initial understanding of the disease progression in carotid and cerebral arteries in MFS. It also presents the potential benefits of mild exercise in improving functional and structural properties of the carotid and posterior cerebral arteries in an MFS mouse model.

**POSTER # 105**

**THE IMPACT OF TAU ON MITOCHONDRIAL FUNCTION ASSOCIATED WITH ALZHEIMER'S DISEASE.** Hernandez BL, Cristofano JA, Tseng J-H. Arizona State University; Arizona Alzheimer's Consortium.

Background: As of 2024, nearly seven million Americans over the age of 65 are living with Alzheimer's disease (AD). Pathologically, AD is defined by amyloid-beta plaques and hyperphosphorylated tau tangles. Previous studies indicate that tau is essential for mitochondrial function, which is compromised in AD, even though the details are unclear. Here, we aim to dissect the mechanism by which tau benefits while disease-associated tau variants compromise mitochondrial function and neuronal health.

Methods: Different types of tau, including wild-type and several disease-relevant variants, were overexpressed in HEK-293 cells to examine tau-mitochondria interaction and associated mitochondrial health. The extent of interaction between different species of tau with mitochondria was analyzed by co-immunoprecipitation and fluorescence microscopy. The quantity of mitochondria was assessed by the levels of several mitochondrial markers. Mitochondrial dynamics was evaluated by the enzymes that promote mitochondrial fusion.

Results: By co-immunoprecipitation and fluorescence microscopy, we observed a direct interaction between tau and mitochondria. In the presence of wild-type tau, the amount of two common mitochondrial markers significantly increases compared with a disease-relevant tau variant. The first marker is COX IV, an enzymatic component of the electron transport chain. Additionally, the level of mitofusin-2, an enzyme critical for mitochondrial fusion, is elevated in the presence of wild-type tau.

Conclusions: These results suggest that wild-type but not disease-relevant tau may have a beneficial role on mitochondrial function and therefore neuronal health by elevating the amount of mitochondria and sustaining mitochondrial dynamics. In addition, targeting tau variants could suppress neurotoxicity and cognitive decline through mitochondrial regulation in AD and other related dementia.

**POSTER # 106**

**BEHAVIORAL AND NEURAL DISSOCIATIONS BETWEEN EPISODIC MEMORY RETRIEVAL SUCCESS AND PRECISION IN HEALTHY AGING AND MILD COGNITIVE IMPAIRMENT.** Hill PF, Markham DC, Garren JD, Ekstrom AD. University of Arizona; Arizona Alzheimer's Consortium.

Background: Episodic memory declines during healthy aging and is often reported as an early symptom of Alzheimer's disease (AD). However, standardized assessments of memory performance are limited in their accuracy to predict progression of early-stage AD pathology. The 'all-or-none' approach commonly used in neuropsychological assessment for quantifying memory performance might miss out on subtle variation in the fidelity or quality of mnemonic representations retrieved from memory.

Methods: Fifty cognitively unimpaired (CU) older adults and 12 older adults with mild cognitive impairment (MCI) completed five study-test cycles of a continuous report item-location memory task. A subsample of 25 participants (22 CU, 3 MCI) performed the task while undergoing high-resolution structural and functional MRI. During the study phase, participants viewed trial-unique objects located around the perimeter of an invisible circle. During the test phase, old and new objects were presented in the center of the screen and participants were instructed to recall the original location of each objects using a continuous analogue response dial to indicate their response. Trial-wise distance error between the remembered and true location of each object were fit with a probabilistic mixture model to estimate two distinct memory processes that are often conflated by categorical response memory paradigms: the ability to accurately retrieve prior details from memory (i.e., retrieval success), and the fidelity of details successfully retrieved from memory (i.e., memory precision).

Results: Behavioral measures of item recognition and associative memory accuracy were significantly reduced in the MCI cohort relative to CU older adults. Measures of memory precision did not significantly differ between the two groups. Critically, we observed substantial individual differences in memory precision that were independent of retrieval success and performance on standardized assessments of verbal and visuospatial memory, and age. Turning to the MRI analyses, we observed a robust positive association between transentorhinal cortex volume and retrieval success. Retrieval success effects were also associated with enhanced fMRI BOLD activity in bilateral hippocampal ROIs. Memory precision effects, by contrast, were associated with enhanced fMRI BOLD activity in posterior occipital and retrosplenial cortices.

Conclusions: Precision-based measures of episodic memory appear to capture subtle changes in cognitive function during early stages of AD progression that cannot be readily accounted for by standardized assessments of verbal and visuospatial memory.

**POSTER # 107**

**SPLICING AND TRANSCRIPTOMIC CHANGES IN MATRIN 3 S85C KNOCK-IN MICE.**
Houchins N, Quezada G, Valentine A, Bakkar N, Bowser B, Medina DX. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Matrin 3 is a nuclear matrix protein that has many roles in RNA processing including splicing and transport of mRNA. Missense mutations in the Matrin 3 gene (MATR3) have been linked to familial forms of amyotrophic lateral sclerosis (ALS) and distal myopathy with vocal cord and pharyngeal weakness (VCPDM)(1) . However, the exact role of MATR3 mutations in ALS and myopathy pathogenesis is not understood. Protein interactome studies have demonstrated that Matrin 3 interacts with numerous proteins involved in RNA processing. Our lab has previously demonstrated that ALS-linked mutations alter MATR3 protein interactions and decrease nuclear export of mRNA. It is important to establish new models to understand the role of Matrin 3 and MATR3 mutations in neuromuscular disease pathogenesis. We hypothesize that MATR3 mutations cause RNA processing deficits which contribute to motor neuron (ALS) and muscle (myopathy) centric disease. Objectives: To elucidate the role of Matrin 3 disease associated mutations on RNA metabolism in vivo.

Methods: We generated novel knock-in mouse models that express the S85C (ALS/VCPDM associated). Importantly, these new knock-in mouse models (generated in collaboration with The Jackson Laboratory using CRISPR-Cas technology) avoid overexpression and maintain physiologic levels of wildtype or mutant Matrin 3. To determine longitudinal phenotypic effects induced by MATR3 mutations, motor and cognitive functions were tested using the rotarod, open field, and novel object recognition assays. CNS and muscle tissue were collected at early and late time points to determine the effects of MATR3 mutations on neuromuscular pathology and transcriptomic changes.

Results: Behavioral analysis demonstrated that homozygous S85C knock-in caused significant motor impairment detectable as early as 3 months of age. At 12 months of age, near natural endpoint, we found that there were a range of transcriptomic changes in various tissues including the spinal cord, cerebellum, cortex, and muscle. Interestingly, these changes occurred in both the heterozygous and homozygous knockin mice. Synaptic and inflammatory related genes were among the most dysregulated. In addition, we detected differential splicing of several genes within the data set CNS tissue.

Conclusions: This study presents pathological and transcriptomic consequences of expressing the S85C matrin 3 mutation in vivo. Importantly, transcriptomic analysis demonstrates that synaptic and inflammatory genes are the most dysregulated. Previous work has demonstrated that matrin 3 levels can influenced by synaptic function. Our findings suggest that matrin 3 may participate in a feedback loop in modulating synaptic function. In addition, we observed widespread splicing changes in various tissues of the CNS. This study suggests a broad role of matrin 3 in influencing RNA metabolism through various mechanisms in vivo.

References: (1) Johnson J, Pioro E, Boehringer A, et al Nat Neurosci. 2014; 17:639–743.

Acknowledgments: We thank the Barrow Neurological Foundation, Flynn Foundation, and NINDS R21 NS116385 for providing support.

**POSTER # 108**

**METABOLIC HEALTH AND INFLAMMATORY MARKERS AS TARGETS FOR HEALTHY COGNITIVE AGING.** Hoscheidt S, Huentelman M, Ryan L. University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Insulin resistance is associated with chronic activation of pro-inflammatory signaling and interferes with cognitive function. Independent and interactive effects of insulin resistance (IR) and pro-inflammatory cytokines on hippocampal and frontal function remains poorly understood, particularly in individuals who harbor a genetic risk for AD, APOEε4. Regulation of normal insulin function in as early as midlife may be instrumental in reducing later risk for developing dementia due to AD, particularly in APOEε4 carriers.

Methods: Cognitively asymptomatic middle-aged adults (N=194, mean age=63.9 years) from the Precision Aging Network, Healthy Minds for Life study, underwent fasting blood draw, neuropsychological and cognitive testing. Relationships between pro-inflammatory cytokines, specifically interleukin 6 (IL6), HOMA-IR, and APOEε4 status were examined. Complex executive function tasks and memory performance was examined with respect to HOMA-IR, IL6, and APOEε4 status.

Results: Higher levels of HOMA-IR were significantly associated with worse performance on the Deary Choice Reaction Time (RT) task ($p=0.004$). Higher levels of HOMA-IR were also significantly associated with higher levels of IL6 ($p=0.005$). Higher levels of IL6 were significantly associated with poorer performance on the delayed AVLT in carriers, but not noncarriers, of APOEε4 ($p=0.029$).

Conclusions: Overall, findings suggest that IR is associated with inflammation, and that these factors play a role in poorer executive and hippocampal function as early as midlife. Findings provide support for targeting insulin function as a potentially modifiable risk factor for AD, particularly in individuals who harbor APOEε4.

**POSTER # 109**

**INTESTINAL MICROBIOTA DYSBIOSIS IN TRANSGENIC ALZHEIMER'S DISEASE MOUSE MODELS.** Jones TB, Chu P, Jones D, Jentarra G. Midwestern University; Arizona Alzheimer's Consortium.

Background: Studies of the microbiota-gut-brain axis are yielding increasingly valuable data relevant to a wide variety of disorders and to our basic understanding of how our microbiomes influence our health and mental status. Intestinal dysbiosis has been associated with many neurologically based conditions, including depression, anxiety, autism, and Parkinson's disease. Notably, dysbiosis of the gut microbiota has been implicated in the development of Alzheimer's disease (AD). Interactions between the microbiota, the enteric nervous system, and the central nervous system are understood to be bidirectional and can affect metabolic, neurological, immunological, and endocrine functions. In the current study, we hypothesized that the gut microbiomes of mice expressing AD-associated transgenes would be different from wild-type mice and that these differences would be retained independent of the environment in which they were housed. We also assessed whether age and sex affected the gut microbiome.

Methods: Three genotypes of mice were used in this study: APOE4, 3xTg, and C57BL/6 mice. Mice were housed 3 mice/cage with all three mice in a cage having the same genotype (control-housed mice) or one mouse of each genotype in a cage (hetero-housed mice). Fecal pellets were collected at 6 weeks, 4 months, and 6 months of age and the intestinal microbiota was assessed via 16S rRNA gene sequencing.

Results: Our data show that at all ages and all genotypes, Firmicutes is the dominant phylum followed by Bacteroidota, although the relative proportions differed somewhat across time and genotype. Actinobacteria was also present in all three genotypes, but at much lower relative abundance. Interestingly, while APOE4 and C57BL/6 mice had a measurable abundance of Verrucomicrobiota that was most prevalent at six weeks of age, this phylum was almost completely absent from 3xTG mice. Analysis at the class level revealed that Bacilli and Clostridia were the dominant classes of Firmicutes in all three genotypes. However, Clostridia was present in greater relative abundance in 3xTg mice at all ages compared to APOE4 and C57BL/6 mice an effect most pronounced in females. With respect to age, there was no change in the predominant phyla in any of the three genotypes, although there were shifts in the relative proportions of each class within a phylum across time. In females that were hetero-housed, there was a distinct shift in the relative abundances of the major phyla such that Verrucomicrobiota disappeared in all genotypes, while Clostridia became more evenly distributed across all genotypes. In hetero-housed males, a similar pattern was observed although the differences were not as notable. At 6 weeks of age, Verrucomicrobiota was present to a greater extent in APOE4 and WT males, however, Clostridia did not predominate in 3xTg males as was observed in females. As the mice aged, Clostridia became more abundant across all genotypes.

Conclusions: In conclusion, our data support a shift in intestinal microbiota in response to co-housing environmental variables, an effect that was more pronounced in females as compared to males. Contrary to our hypothesis, genotype did not prevent adoption of microbiota from cagemates. In control-housed mice the transgenes appeared to play a role in the microbiota that colonized the intestinal tract, however, these differences largely disappeared when mice of different genotypes were co-housed.

**POSTER # 110**

**INTERROGATING THE PROTECTIVE EFFECTS OF NEURONAL RBBP7 ON NEUROINFLAMMATION, AUTOPHAGY AND TAU PATHOGENESIS.** Judd JM, Winslow W, Dave N, Velazquez R. Arizona State University; Arizona Alzheimer's Consortium; Gates Ventures.

Background: Epigenetic dysfunction contributes to the pathogenesis observed in Alzheimer's Disease (AD) and related tauopathies. The lysine acetyltransferase p300, which acetylates histones and other proteins, is aberrantly activated in tauopathies. This activation leads to the acetylation of tau at lysine 280, thereby promoting tau aggregation, and inhibiting critical autophagy protein machinery. Autophagy, the degradation of cellular components and aberrant proteins, is deficient in tauopathies. When p300 acetylates macroautophagy machinery (ATG) proteins 5 and 7, the formation of the autophagosome membrane is inhibited. AD brains with high tau burden display an impaired autophagy-lysosomal pathway (ALP), as measured by disturbances in autophagy end products p62 and LC3-II. p62 is an autophagasome cargo protein – accumulation of p62 signals clearance dysfunction. A decrease in p62 and increase in LC3-II is an indicator of autophagy flux - thus reduced LC3-II signals deficient degradation activity. p300 can thus promote tau pathology by acetylating tau and inhibiting clearance of disease-associated proteins. The Retinoblastoma Binding Protein 7 (Rbbp7) chaperones chromatin-remodeling proteins to their acetylation targets, including p300, and is a component of the Polycomb Repressive Complex 2 (PRC2) that silences neurodegenerative associated genes. We recently found that Rbbp7 mRNA and protein levels are reduced in AD patient brains compared to age-matched controls, and negatively correlate with Braak stage (a measure of tau pathology). We also found a neuron-specific downregulation of Rbbp7 mRNA in AD brains, that negatively correlate with neuronal p300 levels. Further, Rbbp7 is downregulated in the PS19 (P301S) mouse model of tauopathy, and genetically rescuing neuronal Rbbp7 in hippocampal (Hp) CA1 reduces tau acetylation and phosphorylation, protects against neuronal death, and reduces p300 levels. Whether increasing neuronal Rbbp7 rescues deficient autophagy and impacts neuroinflammation has yet to be examined.

Methods: To determine whether increasing neuronal Rbbp7 rescues deficient autophagy, reduces neuroinflammation, and decreases pathological tau hyperphosphorylation by altering p300, we retro-orbitally injected mice with an AAV/PHP.eB-CamkII-Rbbp7 (termed AAV-Rbbp7) in PS19 and NonTg mice at 3.5 months, prior to tau pathogenesis. Tissue was collected at 8.5 months.

Results: AAV-Rbbp7 significantly increased Rbbp7 protein in the Hp while reducing p300 levels. We assessed Atg5, Atg7 p62, and LC3-II, and found ALP markers were dysregulated in PS19 mice compared to NonTg, and the AAV-Rbbp7 in PS19 mice restored protein levels similar to NonTg mice, rescuing deficient autophagy. Phosphorylated tau at Threonine 181 and Serine 396 was decreased by AAV-Rbbp7. A 23-plex cytokine panel showed that AAV-Rbbp7 reduced 15 cytokines in PS19 to NonTg levels, demonstrating a reduction of neuroinflammation.

Conclusions: Collectively, this work demonstrates that upregulation of neuronal Rbbp7 rescues deficient autophagy while also reducing pathological tau burden and neuroinflammation, providing growing evidence that Rbbp7 has significant therapeutic effects for multiple aspects of neuropathology, with implications for tauopathies, including AD.

**POSTER # 111**

**CHARACTERIZING THE GENETIC EXPRESSION PROFILE OF AN ALZHEIMER'S DISEASE RISK GENE TREM2 VARIANT IN A CO-CULTURE MODEL OF ORGANOIDS AND MICROGLIA.** Kamzina A, Leinenweber KE, Aldabergenova A, Huentelman M. Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Microglia cells play a primary role in maintaining homeostasis in human brain by clearing the debris and waste through phagocytosis. In Alzheimer's disease (AD), however, microglia is a double-edged sword which can lead to deleterious outcome contributing to neuronal damage and neuroinflammation, mainly in the disease's later stages. This harmful transition is partly influenced by the microglia receptor, Triggering Receptor Expressed on Myeloid Cells 2 (TREM2). Mutations in TREM2, such as common variant R47H, are associated with an increased risk of AD.

Methods: In this work, we utilize iPSC-derived forebrain organoids and microglia to investigate the inflammatory mechanisms and neurodegeneration linked to this mutation. We grew these organoids for up to day 170 and co-cultured them with microglia. We performed both bulk RNA and single-cell RNA sequencing to analyze the transcriptomic profiles using DESeq and Seurat on R. We observed increased phosphoTau(Thr-231)/total Tau protein expression in older organoids, confirmed by immunoassay (MSD) and immunostaining, which also verified successful microglia integration.

Results: While data collection and analysis for these experiments are still in progress, preliminary results suggest that co-culturing microglia with brain organoids harboring a patient-derived mutation facilitates the identification of genetic transcriptional shifts and molecular pathway activities.

Conclusions: Collectively, these findings provide insights into the molecular dynamics of the TREM2 variant in a controlled, physiologically relevant microenvironment, eliminating the need for animal models. This approach opens new avenues for applying mutation-specific research to enhance our understanding of AD and develop precision medicine strategies and better therapeutic options.

**POSTER # 112**

**DE-RISKING CLINICAL TRIAL DESIGN VIA MODEL-INFORMED DRUG DEVELOPMENT WITH THE CRITICAL PATH FOR ALZHEIMER'S DISEASE CONSORTIUM**. Karten Y, Jacobsen C, Priest E, Stephenson D, on behalf of the members of the CPAD consortium and CPAD Tau PET Harmonization and Surrogacy Working Groups. Critical Path Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: The Critical Path for Alzheimer's Disease (CPAD) consortium serves as a pre-competitive, neutral convenor to generate novel, regulatory endorsed quantitative drug development tools and solutions that are made freely available to the public. These tools accelerate drug development by de-risking key decisions in clinical trial planning.

Methods: Patient-level data from contemporary Phase II and III Alzheimer's disease (AD) clinical trials and observational studies make up the CPAD integrated database. This diverse collection of datasets is harmonized and relevant statistical model specifications (based on cognitive outcomes, biomarker modalities, study populations, etc.) are identified. Disease progression models are then fitted using subsets of the CPAD database matching these specifications. With the fitted disease progression models, clinical trial simulations are then developed by applying clinical trial dynamics such as treatment effect, placebo effect, and dropout. Finally, by altering key trial design parameters such as inclusion criteria, trial length, and visit frequency, we can better understand how trial design decisions affect clinical trial outcomes.

Results: As of June 2024, CPAD's data repository contains 75 studies with 101,398 individual anonymized patient records, with a rich source of key AD biomarkers (biofluids and imaging). Different mixed effects models have been developed with cognitive scales as outcome and different biomarker modalities (e.g., PET + MRI, CSF, and plasma) as baseline predictors. A comprehensive clinical trial simulation tool which builds on these disease progression models has been developed and made available. Additionally, harmonization of tau PET results and their impact on cognition along the Alzheimer's disease continuum have been evaluated.

Conclusions: The precompetitive collaboration pioneered by CPAD is fundamental to the generation of actionable tools for accelerating and advancing AD drug development.

**POSTER # 113**

**INVESTIGATING PUBLIC HEALTH IMPACTS OF CARDIOMETABOLIC DISEASES ON INCIDENT DEMENTIA IN THE MEDICARE POPULATION ACROSS THE UNITED STATES**.

Karway GK, Krzyzanowski B, Killion JA, Faust I, Laurido-Soto O, Sabbagh M, Racette B. Barrow Neurological Institute; Washington University; University of Witwatersrand, Johannesburg, South Africa; Arizona Alzheimer's Consortium.

Background: Understanding the impact of CMDs on incident dementia risk can inform primary preventative measures.

Methods: We leveraged nationwide population-based Medicare claims data to compute the individual and combined population attributable factions (PAFs) of eight CMDs on incident dementia adjusted for age, sex, and race in individuals age 65+ in 2017. We mapped the PAFs at the county level to visualize the geospatial patterns of CMD burden on incident dementia nationwide.

Results: Our study included 756,321 beneficiaries with incident dementia and 20,032,716 controls. The nationwide combined weighted PAFs for the eight CMDs was 37% overall, with hypertension (9.6%) ischemic heart disease (6.7%) and chronic heart failure (5.7%) associated with the greatest attributable fractions of incident dementia cases. The highest PAFs for incident dementia cases attributed to CMDs at the county-level were in the Southeastern U.S.

Conclusions: A substantial proportion of incident dementia cases in the U.S. can be attributed to CMDs, especially in the Southeastern U.S.

**POSTER # 114**

**NEUROFIBRILLARY TANGLES PREDICT DEMENTIA IN PATIENTS WITH CAROTID STENOSIS.** Khakwani KZR, Zahra S, Butt HI, Acosta D, French S, Vitali F, Arias JC, Hillis M, Howell C, Bolakale-Rufai IK, Courtney K, Bedrick EJ, Beach TG, Serrano G, Weinkauf CC. University of Arizona; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: There is growing appreciation that extracranial carotid atherosclerotic disease (ECAD) is associated with dementia risk. Despite this, clinical management of ECAD does not involve evaluation for cognitive outcomes or risk stratification for dementia. One impediment to studying and improving clinical care of this cohort (roughly 10% of adults aged >60) is that factors to identify at-risk ECAD patients are not known.

Methods: The Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) study was used to evaluate clinical and histopathological factors for dementia in subjects with ECAD. The primary outcome (dementia) was defined as a composite of Alzheimer's Disease (AD) and/or Vascular Dementia (VaD) based on a clinical/neuropathological diagnosis. Of 1,234 subjects, those with dementia other than AD and/or VaD were excluded; there remained 111 subjects with ECAD to be evaluated. Logistic regression analysis with 5-fold cross validation was performed to examine the association of key risk factors for dementia including age, sex, cardiovascular risk factors, ApoE genetic status, and dementia biomarkers. The results were expressed in Odds ratios (95% CI). Precision-recall and ROC curves were also generated to evaluate the diagnostic accuracy of dementia prediction models.

Results: Individuals with dementia compared to those without had significantly increased levels of stroke, ApoE4 genotype, and dementia biomarkers for NFT and Aβ. Models of multiple combined risk factors were little or no better than NFT alone, which showed a 96.9% PPV at a NFT level of 10 threshold.

Conclusions: Although we hypothesized that a combination of clinical and histopathological biomarkers would result in the strongest predictive model for dementia, we found that NFT alone had the highest association with and PPV for dementia risk in patients with ECAD. As blood-based assays for NFT quantification become more clinically reliable and available, these data support the possibility that NFT quantification may help identify patients with ECAD at increased risk for dementia.

**POSTER # 115**

**CROSS-SECTIONAL ASSOCIATIONS BETWEEN PHYSICAL ACTIVITY AND CSF BIOMARKERS OF ALZHEIMER'S DISEASE: THE MAYO CLINIC STUDY OF AGING.** Krell-Roesch J, Syrjanen JA, Kremers WK, Algeciras-Schimnich A, Knopman DS, Jack CR, Petersen RC, Racette SB, Woll A, Vassilaki M, Geda YE. Karlsruhe Institute of Technology, Karlsruhe, Germany; Mayo Clinic, Rochester; Arizona State University; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Physical activity is associated with decreased risk of cognitive impairment and dementia. To date, little is known about the associations between physical activity and cerebrospinal fluid (CSF)-derived biomarkers of Alzheimer's disease (AD) among older adults free of dementia.

Methods: Cross-sectional study derived from the population-based Mayo Clinic Study of Aging. Individuals aged ≥ 70 years who were free of dementia completed a questionnaire about their physical activity and exercise patterns during the previous 12 months (late-life) and when they were aged 50-65 years (midlife). We created activity scores based on the frequency and intensity (light, moderate, or vigorous) of each activity. CSF biomarkers (p-Tau181, t-Tau, Aβ42, p-Tau181/Aβ42 ratio) were measured using Roche Elecsys electrochemiluminescence immunoassays. We used linear regression models to examine associations between physical activity / exercise scores during mid- and late-life (predictor variables) and CSF biomarker levels (outcome variables; log-transformed), adjusted for age, sex, and body mass index (BMI).

Results: The sample included 243 persons (60% males; 207 cognitively unimpaired, 36 with mild cognitive impairment). Mean [SD] age was 76.5 [4.7] years and BMI was 27.9 [4.6]; 74 participants were APOE ε4 carriers (3 with missing information). Higher midlife exercise levels were associated with lower p-Tau181/Aβ42 ratio (estimate -0.003; 95% CI -0.0054, -0.0001; p=0.045). Higher midlife total physical activity + exercise levels were also associated with lower p-Tau181/Aβ42 ratio (estimate -0.002; 95% CI -0.0037, -0.0002; p=0.026). Similarly, higher late-life exercise was associated with higher Aβ42 (est. 0.003; 95% CI 0.0004, 0.0056; p=0.026) and lower p-Tau181/Aβ42 ratio (est. -0.004; 95% CI -0.0072, -0.0005; p=0.023); higher late-life exercise of moderate + vigorous intensity was associated with higher Aβ42 (est. 0.004; 95% CI 0.0006, 0.0069; p=0.019) and with lower p-Tau181/Aβ42 ratio (est. -0.004; 95% CI -0.0084, -0.0003; p=0.033); and higher late-life total physical activity + exercise was associated with lower p-Tau181/Aβ42 ratio (estimate -0.003; 95% CI -0.0049, -0.0001; p=0.039).

Conclusions: Our preliminary findings suggest associations between higher levels of mid- and late-life physical activity and exercise with lower neuropathological burden as indicated by CSF-derived biomarkers of AD. Further research using prospective cohort study design is needed to validate these findings.

**POSTER # 116**

**STUDY DESIGN OF THE EVALUATION OF SELF-MEDIATED ALTERNATIVES FOR RISK TESTING EDUCATION AND RETURN OF RESULTS (E-SMARTER): A RANDOMIZED TRIAL FROM THE ALZHEIMER'S PREVENTION INITIATIVE (API) PROGRAM.** Langlois C, Bradbury A, Wood BM, Harkins K, Erickson C, Largent E, Egleston B, Reiman EM, Grill J, Roberts JS, Karlawish J, Langbaum JB. Banner Alzheimer's Institute; University of Pennsylvania; University of California, Irvine; University of Michigan; Arizona Alzheimer's Consortium.

Background: Availability of amyloid modifying therapies will dramatically increase the need for disclosure of Alzheimer's disease (AD) related genetic and/or biomarker test results. The 21st Century Cures Act requires the immediate return of most medical test results, including AD biomarkers. A shortage of genetic counselors and dementia specialists already exists, thus driving the need for scalable methods to responsibly communicate test results. The current study builds off our API Generation Program in which we demonstrated the safety and effectiveness of disclosing APOE via telemedicine to cognitively unimpaired adults.

Methods: 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 test results, as well as to characterize the clinical impact of learning this information. eSMARTER will enroll approximately 600 adults aged 60-80. Participants will be randomized to receive results either via telehealth videoconference or by eHealth platform. Participants randomized to the eHealth arm will be offered either the ADWebPortal or ADChatbot but can switch between platforms or request to speak with a healthcare provider during the sessions.

Results: Study design and available participant demographics will be presented. Participants will complete online assessments evaluating their experience with the disclosure modalities as well as the impact of AD genetic and biomarker results disclosure. Participants complete assessments at baseline, prior to the initial APOE disclosure session, and at approximately 0-2 days, 6 weeks, and 6 months following disclosure. pTau-217 plasma levels will be assessed at 6 months after APOE disclosure. PTau-217 disclosure follow-up assessments will be collected approximately 0-2 days and 6 weeks after disclosure of pTau-217 results.

Conclusions: The eSMARTER study addresses the need for practical and scalable methods to responsibly communicate AD genetic and/or biomarker results. The eSMARTER eHEALTH platforms will be made available to support healthcare providers in returning genetic and/or biomarker results to individuals in clinical and research settings. All data and samples collected will be made available for public sharing.

**POSTER # 117**

**ROBUST PCA WITH TRUNCATED WEIGHTED NUCLEAR NORM AND ADAPTIVE HISTOGRAM EQUALIZATION: A NOVEL METHOD FOR LOW-QUALITY RETINAL IMAGE ENHANCEMENT FOR NEURODEGENERATIVE STUDIES.** Likassa HT, Chen K, Wang Y, Zhu W, Sun D, Dumitrascu O, Chen D. Arizona State University; University of Pretoria; Mayo Clinic, Arizona; Indiana University School of Medicine.

Background: Retinal imaging techniques have been used in the study of neurodegeneration including Alzheimer's disease (AD). They often suffer from sub-optimal quality and artifacts, leading to diagnostic inaccuracies. To address these challenges, we recently developed a robust Principal Component Analysis (RPCA) method that outperformed existing methods (Likassa et al 2024). To further improve our technique addressing the lost detail of the image characteristics, we propose integrating RPCA with Truncated Weighted Nuclear Norm (TWNN) and Adaptive Histogram Equalization (AHE).

Methods: We introduced a novel RPCA method that integrates Truncated Weighted Nuclear Norm (TWNN) with Adaptive Histogram Equalization (AHE) to effectively decompose low-quality retinal images into low-rank and noise components, with the low-rank component representing the enhanced image. TWNN is incorporated into the RPCA method to improve image quality by assigning weights to each retinal image, precisely targeting and eliminating noise and anomalies from degraded images. AHE is employed as a preprocessing step to enhance image contrast and emphasize critical details, such as blood vessels, through local histogram adjustments. This approach is formulated as an optimization problem, and the integration of TWNN and AHE within the RPCA framework is optimized using the Alternating Direction Method of Multipliers (ADMM), which independently updates the parameters involved. To assess its effectiveness and generalizability, we first generated synthetic data by introducing varying levels of noise (5% to 25%) to retinal images. The performance of our method was assessed usinig the synthetic and the real data from EyeQ, diabetic retinopathy, DRIVE and STARE datasets.

Results: Our method significantly outperformed state-of-the-art methods in noise reduction and substantially enhanced the quality of low-quality retinal images. We further evaluated the method on low-quality EyeQ retinal images with corresponding ground truth, where it demonstrated marked improvements over five baseline techniques, producing enhanced images closer to the ground truth. Additionally, evaluations using diabetic retinopathy, DRIVE, and STARE retinal images confirmed that our method surpasses all existing state-of-the-art methods in image quality enhancement. These advancements are reflected in superior performance across key metrics, including Peak Signal Noise Ratio, Relative Absolute Error, Contrast to Noise Ratio, Root Mean Square Error and Cohen's Kappa. The proposed method improved PSNR from 29.62 to 35.25, SSIM from 0.90 to 0.93, and reduced RAE from 0.11 to 0.06 compared to recent baselines with 25% noise added to the retinal images.

Conclusions: We conclude that integrating TWNN and AHE with RPCA results in significant enhancements in low-quality retinal images. This novel method effectively improved image quality and increased diagnostic accuracy in retinal imaging. With additional validation, our approach will be a valuable tool in the study of neurodegenerative disease including AD.

**POSTER # 118**

**NEUROPATHOLOGICAL CORRELATES OF DEMENTIA IN CASES WITH BRAAK NEUROFIBRILLARY STAGE IV.** Lorenzini I, Tremblay C, Aslam S, Beh ST, Walker JE, Intorcia AJ, Arce RA, Borja CI, Cline MP, Qiji SH, Mariner M, Krupp A, McHattie R, Wermager Z, Shull A, Beach TG, Serrano GE. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: The density and neuroanatomical localization of neurofibrillary tangles (NFT) contribute to cognitive impairment. Autopsied subjects with NFTs restricted to subcortical regions may have had no cognitive impairment, mild cognitive impairment, or dementia, whereas subjects with widespread NFTs in neocortex most often have dementia. In this study we aimed to understand why some subjects with NFTs restricted to limbic areas, specifically Braak stage IV, develop dementia, while others do not. We hypothesized that comorbid non-AD pathologies could be contributing to dementia in these subjects.

Methods: Subjects with neuropathological Braak NFT stage IV were selected from the Arizona Study of Aging Neurodegenerative Disorders. We used multiple logistic regression models to predict the presence of dementia or no dementia. Independent variables included Lewy body pathology (LB), cerebral amyloid angiopathy (CAA), cerebral white matter rarefaction (CWMR), argyrophilic grains (ARG), TDP-43, number of microinfarcts and neuritic plaque densities. All models were adjusted for sex and age.

Results: From a total of 394 subjects, 240 were demented and 154 were not demented. Age was not significantly different between groups, while a higher percentage of males had dementia. Demented subjects had higher densities of LB, CAA, neuritic plaques and number of cases with TDP-43. The total number of different pathologies significantly predicted dementia and plaque, LB and CWMR were all significant independent predictors of dementia. When subdividing cases based on their plaque densities, we found that LB, CWMR and ARG were independent predictors of dementia in the low neuritic plaque density group (LPD; zero to sparse), while LB and plaque density predicted dementia in the higher plaque density group (HPD; moderate to frequent).

Conclusions: Braak NFT stage IV subjects with dementia showed higher plaque density, TDP43 pathology, LB stage and density, total tangle score and CAA score demonstrating that mixed pathology is an important aspect of developing dementia.

**POSTER # 119**

**LESS SLEEP DURING THE WAKE CYCLE AFTER REPEATED CLOSED HEAD INJURY.**

Louangprasert K, McQueen KA, Griffiths DR, Lifshitz J. University of Arizona, College of Medicine-Phoenix; University of Arizona; Phoenix VA Health Care System; Arizona Alzheimer's Consortium.

Background: Head injury can disrupt sleep and produce a complex inflammatory response; repeated head injury may produce cumulative effects. However, the cumulative effects of repeated closed head injury on sleep, inflammation, and astrogliosis remains unclear. In our prior study, repeated closed head injury every other day indicated a possible conditioning effect on subsequent head injuries and sleep. In this follow-up study, we hypothesized that either once or twice daily closed head injury would disrupt sleep patterns, particularly during the mouse wake cycle, and increase inflammation, where effect sizes would be cumulative with subsequent injuries.

Methods: Male C57BL/6J mice (n=12) were randomly assigned to either once daily (ZT=3) or twice daily (ZT=3&6) weight drop head injury (Height: 94cm, Weight: 100g) allowing free head rotation daily for five consecutive days. Mice were anaesthetized and weight drop was administered upon normal respiration. Mice were immediately monitored for righting reflex recovery time and returned to non-invasive piezoelectric sensor sleep recording chambers. Sleep was recorded hourly from ZT=12 to ZT=2 and analyzed for sleep density, defined as sleep percentage per hour during the animal's wake cycle. Next, brains from a subset of animals from each injury group (n=3) were sectioned in the coronal plane and regions of interest were stained with anti-GFAP or anti-Iba1 antibodies to characterize astrogliosis and inflammation respectively. Regions of interest were GFAP-positive cells in the CA1, CA3, and DG regions of the hippocampus and Iba1-positive cells in the S1BF region of the cortex. They were evaluated using automated pixel intensity analysis in ImageJ.

Results: No cumulative effects on righting reflex times or sleep were observed across the week for single or repeated injury. The righting reflex times for the second daily injury were longer than the first injury of the day. A decrease in sleep density was seen at post-injury days one ($F(1,20)=34.498$, $p<0.001$) and three ($F(1, 20)=65.613$, $p<0.0001$) compared to baseline. Sleep density at any post-injury timepoint was unaffected by injury group. There were no significant difference in GFAP expression in the hippocampus or Iba1 expression in the S1BF region of the cortex between injury groups.

Conclusions: This study provides insight on the consequences of these repetitive closed head injuries on sleep, inflammation, and astrogliosis. Further studies will explore injury parameters and interactions between repeated head injuries.

**POSTER # 120**

**INTERACTIONS OF VEGF 1154A AND 2578C WITH APOE E4 ON AMYLOID LOAD IN COGNITIVELY UNIMPAIRED OLDER ADULTS.** Malek-Ahmadi M, Piras I, Wang Q, Chen K, Devadas V, Luo J, Su Y. Banner Alzheimer's Institute; Translational Genomics Research Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: Previous studies have shown that carriage of the VEGF 1154A (rs1570360) and the VEGF 2578C (rs699947) alleles may confer a protective effect on the development of Alzheimer's disease (AD). However, it is unknown if these associations are APOE-dependent and whether they can be observed in asymptomatic individuals with varying levels of amyloid pathology. The aim of this study is to determine whether interactions between the APOE ε4 allele, VEGF 1154A, and VEGF 2578C are associated with amyloid load in cognitively unimpaired (CU) older adults.

Methods: Data from 341 CU ADNI subjects (57% female) with a mean age of 74.35±6.94 years and a mean education level of 16.63±2.44 years were included in the analysis. Thirty-two percent (n=109) were APOE ε4 carriers with the following distributions for each VEGF allele: 1154A – GG=165, AG=147, AA=29; 2578C – AA=88, AC=166, CC=87. AV-45 mean cortical standard uptake value ratio (MCSUVR) was used to determine amyloid load. Generalized linear models were used to quantify the main effects of the VEGF alleles and their interactions with APOE ε4 on demographically-adjusted MCSUVR values. Cohen's d effect size was used for groupwise comparisons.

Results: The interaction between VEGF 1154A and APOE was statistically significant (β = -0.02, 95% CI (-0.04, -0.008), p = 0.002). Further analysis among those with two A alleles of VEGF 1154 found that APOE ε4 carriers had substantially lower amyloid load relative to ε4 non-carriers (p = 0.01, d = 1.04). Within APOE ε4 carriers, there were no significant differences among the GG, AG, and AA genotypes. The interaction for VEGF 2578C and APOE approached statistical significance for amyloid load (β = 0.01, 95% CI (-0.001, 0.03), p = 0.06).

Conclusions: Homozygosity for the AA genotype of VEGF 1154 is associated with reduced amyloid load in APOE ε4 carriers and warrants further investigation as a potential protective factor for AD.

**POSTER # 121**

**EFFECTS OF PEROXYNITRITE ON VASCULAR SMOOTH MUSCLE CELL BKCA CHANNELS.** Martin PE, Pires PW. University of Arizona; Arizona Alzheimer's Consortium.

Background: Oxidative stress impairs vascular function in the brain and has been linked to neurodegenerative diseases, such as Alzheimer's Disease (AD). Peroxynitrite is an oxidant produced in the cerebral vasculature via the reaction between superoxide and nitric oxide. A major target of oxidants is the thiol-containing residues of ion channels in the vascular smooth muscle cells, leading to impairment in their function. One of such targets is Ca2+-activated, large-conductance K+ channel (BKCa), which plays a vital role in maintaining cerebral vascular control and is impaired in the 5x-FAD mouse model of AD. However, the direct effects of peroxynitrite on BKCa function remain unknown. We hypothesized that peroxynitrite will decrease BKCa currents in a reversible manner in wild-type and 5x-FAD mice.

Methods: Cerebral arteries of 5-6 month-old C57BL/6J and 5x-FAD mice were isolated and underwent a mild enzymatic digestion to obtain single smooth muscle cells for patch-clamp electrophysiology experiments. Data are means ± SEM, all curves analyzed by 2-way ANOVA with Sidak correction for multiple comparisons, bar graphs by Student's t-test or. Using the inside-out patch clamp electrophysiology configuration, BKCa channel activity was assessed through single channel open probability (Po) after chemical intervention or stepwise increases in membrane voltage.

Results: We observed that peroxynitrite (10 μM) did not alter BKCa voltage sensitivity (PoVehicle = 0.0102 ± 0.0001 vs. PoPeroxynitrite = 0.0105 ± 0.0058, 60 mV, 1 μM Ca2+, P=0.7413). However, peroxynitrite significantly decreased BKCa sensitivity to Ca2+ (in 10 μM Ca2+: PoVehicle = 0.0082 ± 0.0033 vs. PoPeroxynitrite = 0.0013 ± 0.0004, 40 mV, 10 μM Ca2+, P=0.0312). Partial recovery of channel activity was achieved via reducing agent DTT (10 μM, PoPeroxynitrite = 0.0080 ± 0.0020 vs PoPeroxynitrite+DTT = 0.0169 ± 0.0062, 60 mV, 10 μM Ca2+, P=0.0197). Next, we assessed BKCa function in cerebral artery smooth muscle cells from male 5x-FAD mice, and observed that single channel activity is similar to WT littermates (PoWild-type = 0.0430 ± 0.0143 vs Po5x-FAD = 0.0258 ± 0.0058, P = 0.217, 60 mV, 10 μM Ca2+), despite a reported vascular BKCa dysfunction (% Vasoconstriction following iberiotoxin application: Wild-type = 6.600 ± 1.300 vs 5x-FAD = 1.551 ± 0.4645, P=0.0051). Further, in male 5x-FAD mice, channel activity was not improved with DTT treatment (PoVehicle=0.0203 ± 0.0051 vs PoDTT=0.0204 ± 0.0062, 60 mV, 10 μM Ca2+, P=0.9865).

Conclusions: We conclude that peroxynitrite reversibly oxidizes BKCa channels by decreasing the channel's Ca2+-sensitivity, independent of voltage, and that reversible oxidation or other channel modifications are not the root cause of BKCa impairment in male 5x-FAD mice.

**POSTER # 122**

**TECHNOLOGY PREFERENCES OF INDIVIDUALS WITH MILD COGNITIVE IMPAIRMENT AND FAMILY MEMBERS LIVING IN RURAL COMMUNITIES: A MIXED-METHODS STUDY**.
McCarthy MJ, Cerino ES, McCoy MC, Martinez M, Seaton TJ, Goldtooth AD, Livingston RA, Dopson R. Northern Arizona University; Arizona Alzheimer's Consortium.

Background: Digital health technologies hold promise for early detection and support of individuals and family members contending with Mild Cognitive Impairment (MCI), which may be an early step in the progression toward Alzheimer's disease. These technologies may be especially relevant for care dyads living in rural communities who are often isolated, under-resourced, experience geographic barriers to care, and lack basic access to health information and services. The purpose of this study was to explore the technology preferences of rural MCI care dyads in order to better understand the feasibility and acceptability of these technologies for intervention development and delivery.

Methods: We used a mixed methods approach with semi-structured interviews based on Renaud and Biljon's Senior Technology Acceptance Model, conducted with 16 individuals with MCI and their family members. These data were combined with survey data about participant technology preferences, access, knowledge, and use. A subsample of 8 individuals with MCI also participated in a 14-day mobile protocol assessing psychosocial and cognitive health across two weeks of everyday life, providing important process feedback to improve future implementation.

Results: Qualitative data suggest that there is general interest in technology among rural care dyads experiencing MCI. However, comfort levels with specific technologies vary due to demographic, social, economic, personal, structural, and other factors. Survey data corroborate these findings with most participants indicating agreement about the usefulness of technologies for MCI detection and support, as well as access to and knowledge of these technologies. Feedback from mobile protocol participants provided insight into implementing the protocol for rural participants with MCI, including needed training modality (e.g., remote administration vs. in-person at community partner sites) and considerations for maximizing protocol adherence.

Conclusions: Digital health technologies are feasible and acceptable for rural MCI dyads, although the success of this approach may depend upon overcoming identified barriers to use. Additional engagement with these communities is needed in order to optimize these technologies for underserved rural communities, including the potential of an auxiliary live peer or professional support component.

**POSTER # 123**

**ENGAGING RURAL SENIOR CENTERS TO SUPPORT COGNITIVE HEALTH: LESSONS FROM THE NORTHERN ARIZONA MEMORY STUDY.** McCoy MC, Cerino ES, McCarthy MJ, Martinez M, Lucero L, Seaton TJ, Goldtooth AD, Livingston RA. Northern Arizona University; Joe C. Montoya Community & Senior Center; Arizona Alzheimer's Consortium.

Background: Academic-community partnerships grounded in community-based participatory research (CBPR) methods can further health equity related to cognitive health for older adults and caregivers in rural communities. Senior community centers, specifically, can serve as potential partners for the development of preventative memory screening and early interventions to address cognitive health among older adults and provide support for caregivers. The purpose of this poster is to offer a model for researchers in the early stages of partnership development aspiring to engage CBPR approaches to better align their activities with the needs of communities.

Methods: We describe the process of engaging senior centers and community centers serving older adults as research partners to advance the Northern Arizona Memory Study, a mixed methods study designed to develop accessible, culturally informed, and scalable intervention technologies and resources to support rural care dyads with subjective cognitive decline and/or mild cognitive impairment. Drawing upon descriptive findings from surveys with 6 senior center leaders and thematic analysis of study team tracking and notes documenting partnership development, we share lessons learned, barriers, and offer a conceptual model for early-stage partnership engagement aligned with CBPR principles.

Results: Early-stage partnership development lessons learned include the importance of sharing mutual expertise, the value of informal engagement with senior center staff and participants to build trust and rapport, and the role of "word of mouth." Contextual factors related to rurality also impact both the logistics of developing partnerships (such as travel distances in rural communities) and the capacity of centers to partner (for example, due to limited staffing and/or resources).

Conclusions: Senior centers serving rural communities are interested in collaborating with researchers to support cognitive health. However, logistical and capacity barriers may limit the extent to which centers can commit to CBPR partnerships with academic institutions. Consideration of contextual factors unique to the individual community is necessary, requiring researchers to be adaptable and to tailor approaches within each senior center rather than adopting a one-size-fits-all approach to community engagement.

**POSTER # 124**

**APOEε4 GENOTYPE ALTERS MYELIN INTEGRITY IN FRONTAL CORTEX WHITE MATTER DURING THE PROGRESSION OF ALZHEIMER'S DISEASE.** Moreno-Rodriguez M, Perez SE, Mufson EJ. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: APOEε4 allele is the strongest genetic risk factor for Alzheimer's disease (AD) and is associated with a decrease in myelin in the white matter (WM) and cognitive decline. APOE is a lipidic transport protein produced mainly by astrocytes involved in the maintenance of brain lipid levels. The effect that the ε4 allele has upon APOE in astrocytes and cellular components supporting myelination remains incompletely understood.

Methods: Here, we used antibodies against APOE and Olig2 to quantitate the number of astrocytes and oligodendrocytes, respectively, in WM of the frontal cortex (FC). Myelin integrity in WM was determined by optical density (OD) measurements of the luxol fast blue (LFB) stain and myelin basic protein (MBP) immunoreactivity. FC tissue was obtained from APOEε4 carriers and non-carriers that died with an antemortem clinical diagnosis of no cognitive impairment (NCI), mild cognitive impairment (MCI), and mild to moderate Alzheimer's disease (AD) from the Rush Religious Orders Study.

Results: Qualitatively, APOE-labeled astrocytes were virtually absent in the WM of APOEε4 non-carriers, in both NCI and MCI cases, but were slightly more abundant in AD. However, APOE-labeled astrocytes were observed in APOEε4 carriers in all clinical groups, showing significantly higher numbers in MCI compared to non-carriers. Olig2-positive cell numbers significantly decreased in AD compared to NCI in carriers and non-carriers. A within group analysis revealed significantly greater number of Olig2-positive in MCI non-carriers compared to carriers. MBP OD values were significantly higher in MCI APOEε4 non-carriers compared to both NCI non-carriers and MCI carriers. Like MBP, LFB OD values were significantly greater in MCI compared to NCI among APOEε4 non-carriers. By contrast, APOEε4 carriers displayed higher LFB OD values in NCI compared to AD, which were significantly lower than NCI non-carriers. LBF OD measurements positively correlated with global cognition, visuospatial, and episodic memory across groups. Additionally, MBP OD measures correlated with episodic memory and global cognition in the MCI and AD groups.

Conclusions: The presence of APOE astrocytes in the WM of APOEε4 carriers suggests a defect in the ability of these cells to transport APOE required by oligodendrocytes to maintain myelin integrity. In summary, APOEε4 astrocytes in the WM are susceptible to degenerative changes in APOEε4 carriers compared to non-carriers during the progression of the disease.

**POSTER # 125**

**COLLABORATING TO IDENTIFY AND REDUCE HIGH-RISK MEDICATION USE IN GERIATRICS.** Moyer D, Johnson K, Greiwe L, Patterson T. HonorHealth.

Background: Polypharmacy and high-risk medication use in the elderly can lead to avoidable patient harm. Natural physiologic changes that occur with aging put older patients at risk for adverse drug events from medications required for their medical problems. The complexity of our current healthcare system, involvement of several prescribers in a patients' care, along with common ailments such as dementia, make it challenging for patients in this age group to keep track of their medications and take them appropriately. In addition, many patients are taking potentially dangerous over-the-counter medications along with their prescribed medications. These things, combined with limited time during office visits to address elderly patients' medical co-morbidities, make it challenging for primary care physicians to spend time on a detailed medication reconciliation process. Studies have shown that a multi-disciplinary approach to medication reconciliation can lead to decreased use of inappropriate medications in the elderly. Processes with a high degree of pharmacist or pharmacy staff involvement in medication reconciliation have proven to be the most effective.

Methods: This was a quality improvement project completed in an ambulatory Geriatric practice. Our AIM statement was to implement a collaborative medication reconciliation process with our pharmacy team within one month and reach a target of 70% within 3 months of project initiation. Additional goals of our project were to improve identification and decrease use of potentially dangerous medications and to identify opportunities for deprescribing in patients 65 and older. Our project was conducted in 2 PDSA cycles. Each cycle took place over a 6-week timeframe. During the first cycle, our ambulatory pharmacy team reached out to patients scheduled with Dr. Moyer and completed a medication reconciliation. They reviewed over the counter medications, reviewed confusion about medications and doses, and identified the person managing medications. A final medication list and note was compiled and sent to Dr. Moyer before the scheduled visit. During the second PDSA cycle the same steps were completed as described above. In addition, a clinical pharmacists identified Beers list medications, potential interactions, opportunities for deprescribing, and any other considerations for Dr. Moyer review.

Results: Our team was successful at implementing a pharmacist-led medication reconciliation process during the project timeframe. An average of 70% of our scheduled patients underwent this process prior to their visit. A total of 22 patients had a medication reconciliation completed. Out of those, 15 potential drug interactions were identified. There were 33 opportunities for deprescribing, and 20 Beers list medications identified as well. In addition, the pharmacist was able to address confusion over medications in multiple patients, find cost-saving opportunities, and identify numerous over the counter medications that weren't previously on patient lists.

Conclusions: When Geriatricians have access to an ambulatory pharmacy team, this QI project design could serve as a model to implement a pharmacist-lead medication reconciliation process. In addition, this project demonstrated that a pharmacist-led medication reconciliation process can be a successful way to potentially improve prescribing practices in this vulnerable population.

**POSTER # 126**

**EXPLORING WHITE MATTER MICROSTRUCTURAL ALTERATIONS IN MILD COGNITIVE IMPAIRMENT: A MULTIMODAL DIFFUSION MRI INVESTIGATION UTILIZING DIFFUSION KURTOSIS AND FREE WATER IMAGING.** Nelson MR, Keeling E, Stokes AM, Bergamino M.
Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: Mild Cognitive Impairment (MCI) is a transitional phase between normal aging and dementia, and early detection is crucial to prevent or slow the progression to dementia. Advanced diffusion MRI (dMRI) techniques help identify early signs of axonal degeneration and myelin breakdown in MCI. This study used the Alzheimer's Disease Neuroimaging Initiative (ADNI) database to compare white matter microstructure in MCI and cognitively normal (CN) individuals. The results demonstrated the effectiveness of multimodal advanced dMRI in detecting early microstructural changes in MCI, providing insights into the neurobiological mechanisms of cognitive decline.

Methods: The multi-shell dMRI datasets used in this study were obtained from the ADNI database and acquired with a 3 Tesla Siemens Prisma scanner. The study cohort included 55 CN participants (39 females; mean age = 76.1 years, SD = 7.0) and 46 MCI patients (16 females; mean age = 74.2 years, SD = 7.6). Mini-Mental State Examination (MMSE) scores were also available for all participants. Advanced dMRI analyses included the free water imaging (FWI) multi-shell algorithm, diffusion kurtosis imaging (DKI), and the mean signal diffusion kurtosis imaging (MSDKI). A Student's t-test within a linear model evaluated voxel-based differences in diffusion metrics between groups, adjusting for age, sex, normalized volume of white matter hyperintensities (WMH), and average absolute motion. Voxel-based correlations between diffusion metrics and MMSE scores were analyzed using the same covariates. Data analysis was conducted using an in-house R script and Rstudio. The Threshold-Free Cluster Enhancement (TFCE) method was applied to ensure robust clustering without arbitrary thresholding, and multiple comparisons were controlled using a Family-Wise Error (FEW) correction with the Benjamini-Hochberg procedure (FDR < 0.05). Effect sizes were quantified using Hedges' g, with $|g| \geq 0.61$ indicating a large effect for group differences, and Spearman's correlation coefficients $|\rho| > 0.44$ marking significant effects for correlations with MMSE.

Results: No significant differences in age were found between groups (Student's t-test: $t = -1.162$; $p = 0.248$), but significant differences were observed in MMSE scores (Mann-Whitney U test: $W = 1621$; $p = 0.003$). The MCI group had significantly higher free water levels in the corpus callosum and right cerebellar peduncle, along with decreased kurtosis values in several white matter areas, compared to the CN group. These results indicate neuroinflammatory responses and microstructural disruptions in the MCI group. Additionally, negative correlations between MMSE scores and free water levels in the MCI group underscore their potential as early biomarkers of cognitive impairment.

Conclusions: This study examined the intricate relationship between diffusion metrics and cognitive status in CN and MCI participants, revealing that white matter microstructural changes through advanced diffusion imaging can serve as early indicators of cognitive impairment. These findings indicate that multimodal diffusion MRI techniques offer new insights into the neurobiological mechanisms of cognitive decline, highlighting the importance of advanced imaging in early detection.

**POSTER # 127**

**EXPLORING NEUROGENOMIC DISORDERS THROUGH ORGANOID GENERATION.**

Nicholson L, Mosqueda Crespo M, Kamzina A, Taguinod F, Beres S, Piras IS, Huentelman MJ. Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Neurological disorders affecting healthy aging and cognitive quality are difficult to model in vitro and are therefore inadequately diagnosed and treated. Traditional drug development and clinical trial models are similarly impacted in these cases, suggesting a need for a personalized approach. Organoids are self-organized, 3D cultures, and are derived from iPSCs which can be differentiated to study an organ of choice. Brain-specific organoid generation allows for reproducible and versatile modeling of neurodevelopmental processes and associated disorders.

Methods: We successfully created patterned forebrain neural organoids differentiated from iPSCs containing CRISPR-generated point mutations first identified in patients with rare childhood brain disorders. Five mutated iPSC lines, and one wildtype control, were used to generate neural organoids and investigate genotype-phenotype changes when compared to control organoids over a 100-day period. Immunofluorescence, RT-qPCR, and single-cell sequencing was performed to validate both the successful differentiation of different region-specific neuronal cell types and confirm phenotypic differences related back to disease presentation.

Results: Immunofluorescence of sectioned organoids confirmed mature neuronal differentiation, as well as region specific brain structures. Single cell sequencing confirmed mutation-specific phenotypic changes in disease-specific targets. Additional organoid protocols have also been optimized by our group for neuroinflammation study and age-related vascular study. Microglia have successfully been introduced into iPSC generated neural organoids and characterized for future immune-infiltration neurological studies. Additionally, blood vessel organoids have similarly been optimized and validated using iPSCs containing genetic mutations associated with neurovascular disorders and Alzheimer's disease.

Conclusions: The optimization of neural, vascular, and immune organoid generation from iPSCs that contain cognitive and age-related mutations represents a promising approach to studying these diseases in vitro. Additionally, the high-throughput capability of organoid study while being able to study genotype-phenotype differences in an environment that more closely resembles the true microenvironment than current monolayer techniques allows for a personalized treatment approach.

**POSTER # 128**

**EXAMINING HEALTH SCIENCES STUDENT ATTITUDES AND KNOWLEDGE OF THE PRIMARY PROGRESSIVE APHASIA (PPA) SYNDROME: A PILOT SURVEY STUDY.** Nickels K, Abraham E, Kielar A. University of Arizona; Arizona Alzheimer's Consortium.

Background: Primary progressive aphasia (PPA) is group of rare neurodegenerative syndromes (affecting <200,000 people in the US) characterized by the progressive decline of language function associated with cortical atrophy of the left-lateralized language network. Despite the establishment of clinical, neuroimaging, and neuropathological diagnostic criteria, it has been documented that individuals with PPA face challenges in the detection and management of their conditions, including misdiagnosis. Prior research suggests that students pursuing medical professions demonstrate poor knowledge of dementia in addition to an overall negative bias toward older adults with dementia. To our knowledge, however, student attitudes and knowledge of PPA have not been directly explored. In this study, we developed and distributed a survey to examine current knowledge and attitudes about PPA among students at the University of Arizona who plan to enter health or communication-based professions.

Methods: Previously validated aging and dementia scales were administered via a Qualtrics XM survey along with new items developed for PPA assessed with Likert-style questions. Items for PPA were divided into two scales: (1) the PPA Knowledge Scale (PPAk), with "knowledge" defined as factual awareness and familiarity with the symptoms of PPA and assessed with true/false statements; and (2) the PPA Attitudes Scale (PPAa), with "attitude" divided into the domains of cognitive, behavioral, and affective components. Three experts in PPA from the University of Arizona provided written feedback on the initial set of PPA items. Survey items were revised, and finalized PPAa and PPAk scales were established. The final questionnaire was shared with faculty who taught courses in the University of Arizona Physiology and Speech, Language and Hearing Science Departments for distribution to students.

Results: A total of 149 students at the University of Arizona responded to the Qualtrics survey. Approximately 91% of respondents were undergraduate students (pre-health = 46%, communication sciences = 29%, neither = 24%). We found a significant difference in PPAa scores between the three tracks of study. Students in communication sciences had the highest PPAa score average (85%), followed by students on the pre-health track (82%), indicating more positive attitudes. Knowledge of PPA did not differ significantly across majors (avg. accuracy = 75%). Scores on the PPAa scale correlated significantly with both attitudes towards aging and attitudes towards dementia. Scores on the PPAk scale correlated significantly with scores for knowledge of aging and knowledge of dementia. The attitudes towards PPA were predicted by attitudes towards dementia and class level, while knowledge of PPA was significantly predicted by knowledge of aging and attitudes towards PPA.

Conclusions: The results of this study provided initial evidence for the reliability and validity of the PPAa and PPAk tools. Our pilot survey found that while attitudes toward PPA were generally positive among students, communication science students had more positive attitudes. However, knowledge was low in all student groups. Our future research plans to explore further validation of the PPAa and PPAk tools and investigate factors that contribute to knowledge of PPA among students who intend to pursue medical professions, with the hope of improving outcomes for individuals contending with progressive language loss.

**POSTER # 129**

**CORRELATION OF AUTONOMIC DYSFUNCTION WITH LEWY BODY PATHOLOGY.** Noe KA, Surdyn M, Adler CH, Mehta SH, Lorenzini I, Walker JE, Theng Beh S, Arce RA, Qiji SH, Intorcia AJ, Borja CI, Cline MP, Krupp AN, McHattie RD, Wermager ZR, Shull A, Mariner MR, Aslam S, Tremblay C, Beach TG, Serrano GE. Banner Sun Health Research Institute; Mayo Clinic College of Medicine.

Background: Parkinson's Disease (PD) is the second most common neurodegenerative disease after Alzheimer's Disease (AD) (Parkinson's Foundation, 2024). Visible symptoms of PD include stiffness, tremors, and slowed body movements. However, nonmotor manifestations can begin much earlier than those of motor dysfunction (Adler & Beach, 2016). To grade and analyze autonomic dysfunction in PD, Visser, et al (2004) developed a self-reported questionnaire, the Scales for Outcomes in Parkinson's Disease (SCOPA), which breaks down six domains in the body: gastrointestinal, urinary, cardiovascular, thermoregulatory, pupillomotor, and sexual functioning. In this study we analyzed data from the Brain and Body Donation Program (BBDP) to see if autonomic dysfunction correlates only with Lewy body (LB) pathology in the brain or if AD pathology might also predict autonomic dysfunction.

Methods: Participants enrolled in the Brain and Body Donation Program (BBDP) that came to autopsy and had full pathological assessments were used for this study. Data was extracted from the BBDP database from participants who answered the SCOPA questionnaire at least once (n=790). The total SCOPA scores, domain summation, and individual questions were correlated with LB and AD pathology scores, as well as basic demographics such as age at assessments and years of neurological disease. Pathological data included pathology scores by brain regions, summations of the scores, and staging of disease. All correlations and group analyses were done using Graph Pad Prism.

Results: Gender did not seem to correlate with or directly affect autonomic dysfunction. LB pathology showed more robust correlation with multiple autonomic dysfunction domains than AD pathology. LB pathology in the substantia nigra correlated the most with different autonomic domains and total scores. The autonomic manifestations with the highest correlation with the brain LB pathology were salivation, constipation, strain, fainting, lightheadedness while standing, and urine loss, all of which are commonly seen in PD patients. The temperature regulation category and eye oversensitivity to light were least significant with AD pathology and LB distribution in the brain regions.

Conclusions: Our results show that autonomic dysfunction has a higher correlation with LB pathology than AD pathology. Pathology in the substantia nigra, which is responsible for coordinating movement and muscle tone, was found to correlate the most with symptoms of autonomic dysfunction. Furthermore, specific autonomic symptoms (i.e. salivation) are affected more in PD patients than other cases.

**POSTER # 130**

**FRONTAL CORTEX SPLICING PROTEIN U1A AND TAU PATHOGENESIS IN DOWN SYNDROME WITH AND WITHOUT ALZHEIMER'S TYPE DEMENTIA.** Perez SE, Miguel JC, Mufson EJ. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Down syndrome (DS) people have an increased risk of developing Alzheimer's disease (AD) type dementia and by age forty exhibit significant tau containing neurofibrillary tangles (NFTs) and Aβ plaques. However, not everyone with DS develops dementia. We reported that DS with dementia (DSD+) display a greater number of NFTs consisting of a more advanced tau pathology compared to those without dementia (DSD-) in the frontal cortex (FC) suggesting differences in tau pathobiology. Recent evidence suggests that alterations in the splicing protein small nuclear ribonucleoprotein U1A play a role in tau pathogenesis in AD and DS.

Methods: We examined U1A nuclear protein levels, size and counts as well as phosphorylated AT8 tau, 3Rtau and 4Rtau containing neurons and amyloid plaque load in layers III and V-VI in the FC of demented (n=22) and non-demented (n=12) people with DS.

Results: We observed intense nuclear U1A immunostaining in layers III and VI in all DSD-, while DSD+ cases also displayed pale immunostaining across layers. The number of intense U1A stained nuclei was significantly greater in layer III in DSD- compared to DSD+. By contrast, the number of nuclei displaying weak U1A labeling was significantly increased in layer III in DSD+ compared to DSD-. In DSD+, optical density (OD) measurements of lightly immunoreactive U1A nuclei were significantly reduced compared to more intensely reactive U1A labeled nuclei in layers III and V-VI. Nuclear area of lightly stained U1A was smaller than the more intensely immunostained in layer III in DSD+. Cytoplasmic mislocalized U1A reactivity had either a fine granular or tangle-like appearance in DSD+ cases, which was similar in number between layers. FC AT8, 3Rtau and 4Rtau positive NFT counts were significantly higher in DSD+ than in DSD- in layers III and V-VI, while plaque load was unchanged between groups. Correlational analysis revealed that weak nuclear U1A OD values, nuclear area, and counts were strongly associated with AT8 and 3Rtau NFTs, but only with layer V-VI 4Rtau NFTs and layer III plaque load across clinical groups. Mislocalized U1A tangles showed the strongest association with 4Rtau NFT counts in both layers across groups. Similar changes in U1A measures and associations with NFTs were not observed between intensely reactive nuclei across groups.

Conclusions: These findings suggest that FC U1A nuclear pathogenesis is greater and show a stronger relationship with tau than plaque pathology which contributes to the onset of dementia in DS.

**POSTER # 131**

**IDENTIFICATION OF CANDIDATE RNA BLOOD BIOMARKERS IN ALZHEIMER'S DISEASE BY PSEUDOTIME ANALYSIS.** Piras IS, Song S, Naymik M, Ecca F, Huentelman MJ.
Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: The goal of this study is to identify RNA blood biomarkers capable of predicting Alzheimer's Disease (AD) onset. The development of blood biomarkers would enhance the ability to screen for AD and monitor its progression. Additionally, these biomarkers would help identify prodromal stages of AD, facilitating more efficient treatment and timely inclusion of patients in clinical trials. Current validated AD biomarkers include: Amyloid-beta and tau positron emission tomography (PET), ratio of 1-42 and 1-40 amyloid-beta peptides in cerebrospinal fluid (CSF), and concentration of total tau and phosphorylated tau in CSF. However, these procedures are invasive, expensive and time-consuming.

Methods: In this study we applied pseudotime analysis, a machine learning-based algorithm designed to extract latent temporal information from cross-sectional expression profiling data. The samples are ordered according to a molecular progression that correlates with the disease severity. The datasets analyzed included blood transcriptomic profiling from the AddNeuroMed cohort, available on Gene Expression Omnibus (GEO) (GSE63060 and GSE63061; n = 717 AD and controls (CTL)). Post-mortem brains transcriptomic profiling from eight brain regions from the Accelerated Medicine Partnership-AD (AMP-AD, RNA harmonization study; #syn21241740; brain regions: ACC, DLPFC, FP, IFG, PCC, PHG, STG and TCX; n = 878 AD and CTL donors) were used to assess the association of candidate biomarkers with pseudotime, neuropathological and clinical variables. These data are part of the Mayo, Mount Sinai and ROSMAP studies.

Results: We first extracted the pseudotime trajectories using the DDRTree method from two independent blood RNA profiling datasets from the AddNeuroMed cohort, using a number of components to include 95% of the variance. We identified a significant association of pseudotime with the clinical diagnosis in both GSE63060 and GSE63061 datasets (Wilcoxon Rank Sum Statistic: $P < 5.3E-05$). We detected 3,704 genes associated with pseudotime in both datasets, and following the same log2 FC direction ($|r| >= 0.4$; Benjamini and Hochberg (BH) adj-$p < 0.05$). Next, we conducted pseudotime analysis on the post-mortem brain, extracting the trajectories using the phenoPath method. We correlated the pseudotime with clinical and neuropathological variables (Clinical Dementia Rating, Braak stage, disease status, and amyloid plaque density), identifying significant associations in 83.8% of the variable/pseudotime comparisons. Then, we identified 866 genes significantly correlated with pseudotime, with concordant directions across all eight brain regions ($|r| >= 0.4$; Benjamini and Hochberg (BH) adj-$p < 0.05$). These 866 genes were used to validate the results found in the blood data (AddNeuroMed cohort), and after cross-referencing the results we identified an overlap of 112 genes significantly associated in both blood and post-mortem brains ($|r| >= 0.4$; BH adj-$p < 0.05$). These 112 genes showed a correlation with pseudotime in both blood and across 8 brain regions, also correlating with the clinical diagnosis and neuropathology.

Conclusions: In conclusions, our results highlighted a set of genes that might represent top candidates for further validation in longitudinal cohorts to predict the AD onset. These results are relevant as the current validated AD biomarkers are invasive, expensive and time consuming.

**POSTER # 132**

**CELLULAR AND MOLECULAR PHENOTYPES OF DEMENTIA WITH LEWY BODIES VERSUS PARKINSON'S DISEASE WITH DEMENTIA.** Preller K, Antone J, Alsop E, Gittings L, Song S, Beach T, Serrano GE, Pirrotte P, Piras IS, Van Keuren-Jensen K, Sattler R. Barrow Neurological Institute; Translational Genomics Research Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Lewy Body Dementia (LBD) serves as an umbrella term for Dementia with Lewy Bodies (DLB) and Parkinson's Disease Dementia (PDD). While not much is known about the differences in mechanisms of disease pathogenesis, these diseases present with similar symptoms that differ mostly in their onset. PDD has motor symptoms that manifest a year before any cognitive impairment, while DLB patients have cognitive impairment and hallucinations before the onset of motor symptoms. This strongly suggests that there are cellular and molecular differences during disease progression which could be utilized to appropriately diagnose and treat both disorders.

Methods: To cellularly and molecularly define LDB, we applied two human model systems: (1) patient-derived induced pluripotent stem cells (iPSCs) differentiated into cortical forebrain neurons (iPSC-CN), and (2) postmortem DLB and PDD brain tissue samples. For the latter, brain tissue sections from the middle temporal gyrus (MTG) and/or middle frontal gyrus (MFG) (6 PDD, 6 DLB, 6 non-neurological controls (NC), total of 24 samples) were processed for snRNA sequencing (snRNAseq), followed by comparative bioinformatics analyses of differentially expressed genes (DEGs) between the three experimental groups. iPSC-CN (4 DLB; 4 NC) were differentiated and examined for the temporal progression of cellular and molecular alterations using ICC, qPCR, and ELISA. In addition, temporal proteomic and transcriptomic signatures were obtained.

Results: Using 10xGenomics snRNAseq, we obtained, after quality controls and filtering using scanpy, a total of 188,770 cells. These cells were clustered using UMAP dimensionality reduction, which resulted in 19 clusters at a resolution of 0.3. Using canonical markers for broad classification, we identified the major cell types as follows: oligodendrocytes (42.0%), excitatory neurons (ExN; 27.9%), inhibitory neurons (InN; 11.2%), astrocytes (8.9%), microglia (5.5%), oligodendrocytes precursor cells (4.1%) and endothelial cells (0.3%). Differential expression analysis in MTG revealed the largest dysregulation in excitatory and inhibitory neurons in both PDD and DLB compared to the CTL, with the majority of genes underexpressed in the disease group. We detected several differentially expressed genes (DEGs) in all other cell types, mostly overexpressed in the disease group. The top DEGs in the DLB vs CTL comparison were TMEM59L, CNTNAP5, underexpressed in ExN and InN, respectively. The top DEGS in PDD vs CTL comparison were GOLT1B (underexpressed ExN), CADM2 (overexpressed InN), and NRXN3 (underexpressed in oligodendrocytes). In addition to the brain tissue analyses, we have successfully differentiated iPSC-CNs and harvested cell lysates at three different maturation time points for multi-omics analyses. Furthermore, we evaluated temporal occurrence of alpha-synuclein proteinopathy in addition to tau and amyloid pathology-associated cellular and molecular changes.

Conclusions: These studies reveal for the first time snRNA seq data from PDD vs LBD postmortem brain tissue. We further generated novel temporal multi-omics data sets from LBD iPSC-CNs, in addition to dementia and PD-associated cellular proteinopathies.

**POSTER # 133**

**OPTIMIZING COMPOSITE PET MEASUREMENTS FOR TRACKING LONGITUDINAL TAU ACCUMULATION.** Protas HD, Ghisays V, Luo J, Sohankar J, Lee W, Devadas V, Chen K, Reiman EM, Su Y. Banner Alzheimer's Institute; Arizona Alzheimer's Consortium; University of Arizona; Translational Genomics Research Institute; Arizona State University.

Background: Tangle burden, one of the hallmarks of Alzheimer's Disease, is thought to accumulate and spread throughout the brain in a distinctive pattern starting from the entorhinal cortex following Braak stages as characterized in neuropathological studies. Longitudinal tau PET allows us to investigate in vivo the tau spread in an individual and substantial heterogeneity has been observed in the pattern of tau spread. In this analysis, we examine the statistical power of tau PET measurements in tracking disease progression using data from the ADNI cohort.

Methods: The tau PET measures used in this study included conventional SUVR measures as well as graph theory based network strength measures as we previously reported(Protas 2023). We calculate the slopes of both regional SUVR and strength in 41 MCI and 71 CU participants who had one year, and/or two year follow-up. Statistical power was assessed as the sample size needed to detect a 25% reduction in the rate of tau accumulation, and the power analysis was done for CU and MCI participants separately. The optimal composite measures (from combining up to 6 FreeSurfer ROIs) were determined based on two criteria: 1) having minimal tau accumulation (calculated sample size > 10000) in the A- group to ensure we are looking at AD related accumulation, and 2) having the smallest sample size in the A+ group.

Results: Strength in Amygdala, entorhinal, superior frontal , frontal pole, transverse temporal , and inferior parietal regions gives optimal sample sizes of 134 in A+ CU. In CU A+, SUVR in amygdala, lateral occipital and middle temporal produced an optimal sample size of 173. In MCI, for strength, the sample size is 104(A+) in an optimized region including cuneus, postcentral, superior parietal, temporal pole, and rostral and caudal anterior cingulate. With SUVR the optimal region in MCI was entorhinal, lateral occipital and middle temporal with a sample size of 190(A+).

Conclusions: The optimal composite regional SUVR/strength measure varies depending on the target population and typically combines both early and late Braak stages. Further study is needed to confirm this finding using larger datasets.

**POSTER # 134**

**APOE4 EXACERBATES ASTROCYTIC MITOCHONDRIAL DYSFUNCTION-INDUCED NEUROINFLAMMATION AND NEURODEGENERATION**. Qi G, Mi Y, Yin F. University of Arizona; Arizona Alzheimer's Consortium.

Background: Abundant evidence has documented brain lipid dyshomeostasis as an early and persistent hallmark of Alzheimer's disease (AD). Moreover, a variety of AD risk factors are found directly involved in lipid trafficking and/or lipid metabolism. We previously reported that APOE-ε4 (ApoE4), the greatest genetic risk factor for AD, induces a metabolic shift in astrocytes towards diminished fatty acid (FA) oxidation and elevated lipid droplet (LD) accumulation. In addition, reduced capacity of ApoE4 astrocytes in eliminating and degrading neuronal lipids contribute to their compromised metabolic- and synaptic support to neurons. Our recent work further revealed that disrupted FA degradation by astrocytes is sufficient to trigger progressive neuroinflammation and neurodegeneration resembling human AD. However, whether and how compromised astrocytic FA degradation interacts with ApoE4 in promoting AD onset and progression remains unclear.

Methods: Using a mouse model combining humanized ApoE3 or ApoE4 allele with astrocytic mitochondrial dysfunction (ApoE3-TfamAKO and ApoE4-TfamAKO).

Results: We demonstrated that cognitive impairments induced by astrocytic mitochondrial dysfunction was exacerbated by ApoE4. Consistently, ApoE4-TfamAKO showed reduced hippocampal long-term potentiation, synaptic density and dendrite complexity compared to ApoE3-TfamAKO mice. Moreover, ApoE4-TfamAKO mice exhibited stronger neuroinflammation in terms of microglial activation and reactive astrogliosis. Along with enhanced astrocyte reactivity, ApoE4 also increased accumulations of free FA, triacylglycerol, and astrocytic LDs in the hippocampus and cortex of TfamAKO mice. Relative to ApoE3-TfamAKO mice, ApoE4-TfamAKO mice also manifested demyelination, suggested by diminished density and thickness of white matter tracts and lower expression of the myelin-basic protein (MBP).

Conclusions: These findings support our hypothesis that ApoE4 converges with brain mitochondrial dysfunction at astrocytic FA oxidation in disrupting brain lipid homeostasis and driving neuroinflammation and neurodegeneration in AD.

**POSTER # 135**

**LOW FOOD SECURITY IS RELATED WITH MORE MEMORY COMPLAINTS IN A CLINIC-BASED SAMPLE OF LATINO ADULTS**. Saenz J, Tanner L. Arizona State University; Arizona Alzheimer's Consortium.

Background: Low food security has been linked with both diminished objective cognitive outcomes and lower subjective assessments of cognition in studies across the globe. Subjective memory complaints may be important indicators of memory problems in one's daily life. However, few studies have explored links between low food security and subjective memory in Latinos, despite the higher prevalence of food insecurity in the Latino population. The aim of this study is to investigate potential links between low food security and subjective memory complaints in a sample of Latinos.

Methods: We used the Sangre Por Salud (SPS) data, a sample of Latino adults from a federally qualified community health center in Phoenix, AZ who enrolled 2013-2018. Our analytic sample includes n=2,481 Latinos aged 18-85. Food security was assessed using the Household Food Security Scale and memory complaints were measured using the Frequency of Forgetting Scale. Potential links between low food security and subjective memory complaints were tested using linear regression controlling for demographic factors (age, gender, education, nativity), self-rated health, and social support.

Results: Around 76% of the sample were highly/marginally food secure, with 18% and 6% experiencing low food security and very low food security, respectively. Low food security was more common in the US born and among those with lower social support. In multivariate analyses, compared to the highly/marginally food secure, low food security related with 0.18 standard deviations higher memory complaint ($p<0.001$) whereas very low food security related with 0.37 standard deviations higher memory complaint ($p<0.001$).

Conclusions: Findings suggest an association between experiences of low food insecurity and more frequent memory complaints in Latinos. Subjective memory complaints are related with future cognitive impairment and dementia. Future studies should evaluate the potential cognitive benefits of interventions targeting food insecurity.

**POSTER # 136**

**VALIDATING A BRIEF PERFORMANCE-BASED MEASURE OF COGNITION AND DAILY FUNCTIONING IN OLDER ADULTS**. Schaefer SY, Reed AM, Duff K. Arizona State University; Oregon Health & Science University; Arizona Alzheimer's Consortium.

Background: The Clinical Dementia Rating scale (CDR) is a widely-used cognitive and daily function measure among older adults, and primary outcome for Alzheimer's disease (AD) clinical trials. The CDR, however, is lengthy (~1-1.5 hr), uses both patient and collateral reports, and requires a certified and skilled clinician. Given the time, personnel, and patient burden of the CDR, there is a need for a quick, objective screen that can identify patients with higher cognitive and functional impairment who may warrant further evaluation or qualify for clinical trial enrollment (i.e., prognostic enrichment). To meet this need, we have developed a brief (~5-min) performance-based test that involves spooning two raw kidney beans at once with the nondominant hand from a central home cup to one of three target cups in a simple sequence; higher scores are worse, indicating more intraindividual variability across multiple attempts of the task. Prior work has also shown the prognostic nature of this test, given that more cognitive and functional decline over one year is associated with higher (worse) test scores in patients with Mild Cognitive Impairment and AD. An advantage of our test is that it requires no collateral or clinician, and scores are objective without being subject to floor or ceiling effects. Thus, the purpose of this study was to test the concurrent validity of our performance-based test against the Quick Dementia Rating Scale (QDRS) and estimated global CDR.

Methods: In this study, 171 participants (72 cognitively unimpaired; 53 amnestic Mild Cognitive Impairment; 46 mild Alzheimer's disease) completed the performance-based test, as well as the Quick Dementia Rating Scale (QDRS) for estimating CDR. Multivariate linear regression was used to compare performance-based test scores against QDRS scores, controlling for age, sex, and education. Logistic regression was also used to determine the extent to which performance-based test scores could classify CDR cases as 0 vs. ≥0.5.

Results: The performance-based test significantly predicted global CDR (p=.0002), as well as the QDRS Total (p=.003), Behavioral Subtotal (p=.01), and Cognitive Subtotal (p=.003), after controlling for age, sex, and education. All p-values were False Discovery Rate adjusted. Logistic regression also showed that each point increase in performance-based test scores was associated with a 10% increase in likelihood of impairment (CDR≥0.5) (Odds Ratio=1.10; p=.002; 95%CI= [1.03; 1.17]).

Conclusions: These findings support the use of the performance-based test to quickly screen older adults for subtle cognitive and functional impairment, as well as risk for progressing in the near future. This test could also be used as a complement to plasma biomarkers for selecting participants for AD clinical trial enrollment, and because our test can be administered remotely and unsupervised, it could be used even in decentralized trials where some or all of the trial activities occur at locations other than a traditional clinical trial site.

**POSTER # 137**

**COMORBIDITIES IN EARLY-ONSET SPORADIC VERSUS PRESENILIN-1 MUTATION-ASSOCIATED ALZHEIMER'S DISEASE DEMENTIA: EVIDENCE FOR DEPENDENCY ON ALZHEIMER'S DISEASE NEUROPATHOLOGICAL CHANGES**. Serrano GE, Sepulveda-Falla D, Villegas Lanau CA, White III C, Acosta-Uribe J, Mejía-Cupajita B, Villalba-Moreno ND, Lu P, Glatzel M, Kofler JK, Ghetti B, Frosch MP, Lopera Restrepo F, Kosik KS, Beach TG. Banner Sun Health Research Institute; University Medical Center Hamburg-Eppendorf; University of Antioquia, Medellin, Colombia; University of Texas Southwestern Medical Center; University of California, Santa Barbara; University of Pittsburgh; Indiana University School of Medicine, Massachusetts General Hospital and Harvard Medical School.

Background: Autopsy studies have demonstrated that comorbid neurodegenerative and cerebrovascular disease occur in the majority of subjects with Alzheimer disease dementia (ADD), and are likely to alter the rate of cognitive decline, increasing response variability in clinical trials. Generally, comorbidities have been most studied in late-onset sporadic ADD, so we sought to compare ADD comorbidities between subjects with early-onset sporadic ADD (EOSADD; subjects dying under age 60) versus ADD associated with different types of PSEN1 mutations, the most common cause of early-onset autosomal dominant ADD.

Methods: We ascertained the prevalence of ADD comorbidities in PSEN1 cases derived from the United States (US) as well as from Colombia. Data for EOSADD and US PSEN1 subjects (with multiple different mutation types) was obtained from the National Alzheimer Coordinating Center (NACC). The US cases included subjects with several different PSEN1 mutations while the Colombian cases all had the E280A mutation.

Results: Colombian cases all had the E280A mutation. Of ADD comorbidities, LBD was most common, being present in more than half of all cases in all 3 groups. For TDP-43 co-pathology, the Colombian PSEN1 group was the most affected, at about 27%, vs 16% and 11% for the US PSEN1 and sporadic US cases, respectively. Significant large-vessel atherosclerosis was present in a much larger percentage of Colombian PSEN1 cases, at almost 20% as compared to 0% and 3% of the US PSEN1 and EOSADD cases, respectively. Small-vessel disease, or arteriolosclerosis, was much more common than large vessel disease, being present in all groups between 18% and 37%. White matter rarefaction (WMR) was remarkably common, at almost 60%, in the US PSEN1 group, as compared to about 18% in the EOSADD cases, a significant difference. White matter rarefaction was not assessed in the Colombian PSEN1 cases.

Conclusions: The results presented here indicate that some comorbidities are common even in early-onset ADD subjects and should be considered when planning clinical trials.

**POSTER # 138**

**CONTRIBUTION OF ENDOTHELIN SIGNALING TO AD-RELATED CEREBROVASCULAR DYSFUNCTION**. Silva JF, Pires P. University of Arizona; Arizona Alzheimer's Consortium.

Background: Dysregulation of the cerebral microcirculation, as observed in Alzheimer's disease (AD), can impair vital mechanisms regulating real-time nutrient delivery to the brain, consequently disrupting homeostasis within the neuron's microenvironment. ET-1 is involved in vascular inflammation and oxidative damage. Exacerbated ET-1 production is linked to cardiovascular diseases, such as hypertension, and it may play an important role in Alzheimer' disease (AD)-related vascular dysfunction. However, whether altered signaling to ET-1 contributes to cerebral microvascular dysfunction associated with AD remains unknown.

Methods: Pial arteries and parenchymal arterioles from 6 months-old male and female *5x-FAD* and wild-type (WT) littermates were isolated and studied *ex vivo* using pressure myograph and for mRNA (Cardiovascular Diseases - CVD panel) and microRNA (miRNA panel) quantification using nSolver/NanoString technology. Data are means ± SEM, analyzed by two-tailed *Student*'s t-test for myograph data. Rosalind was used to calculate fold changes and p-values for comparisons using the t-test method of mRNA and microRNA data.

Results: Vasoconstriction response to ET-1 was greater in arteries of *5x-FAD,* pial arteries (ET-1 vasoconstriction: 26.21 ± 1.89 vs 15.77 ± 1.63 %, *5x-FAD* vs. WT, $p<0.05$, N=19) and parenchymal arteriole (ET-1 vasoconstriction tone: 29.25 ± 3.08 vs 18.41 ± 1.79 %, *5x-FAD* vs. WT, $p<0.05$, N=13). Bosentan (10 μM), a pan-ET-1 receptor antagonist, did not alter spontaneous myogenic tone, but it reduced myogenic reactivity of arteries from WT but not from *5x-FAD* ($p<0.05$). Sub-transcriptomic analyses showed that, of the 800 mRNA investigated, 15 were upregulated and 20 were downregulated in *5x-FAD* (logFC > 1.2 or logFC< -1.2 and $p<0.05$). *Edn1* mRNA, which codes pre-pro-ET-1, was downregulated, without changes in ET-1 receptors. Upregulated mRNAs include *Rasgrp1*, *Rapgef4* and *Prkacb*, which are involved in protein kinase signaling. Those genes play a role in regulating intracellular signaling, and they may modify ET-1 vascular response. We observed a strong sex difference in differentially expressed genes (DEGs): in females, there was a total of 72 DEGs in *5x-FAD* (16 upregulated and 56 downregulated, including *Edn1*), whereas only 5 DEGs were observed in male *5x-FAD* when compared to WT littermates (2 upregulated and 3 downregulated). We then assessed expression of 599 miRNA in pial artery lysates from male and female *5x-FAD* and WT littermates. When analyzing miRNA expression and found 13 differentially expressed miRNA (7 downregulated and 6 upregulated). Further analysis and segregation by biological sex showed that all differentially expressed miRNA were from female *5x-FAD* (14 miRNA, 6 downregulated, 7 upregulated), and those include miRNA that regulate intracellular kinases and phosphatases such as mmu-miR-434-3p. No changes were detected in miR-206, a miRNA validated to regulate *Edn1*.

Conclusion: The present results suggest that cerebral microvascular hyper-contractility may not be linked to changes in ET-1 receptors, but rather to intracellular mechanisms regulating contractility, including kinases and phosphatases. Further, we observed a strong sex difference in DEG for CVD-related genes and miRNAs.

Funding: Arizona Alzheimer's Consortium Pilot Project grant program (to JFS), NIH (R01AG073230 to PWP) and Alzheimer's Association (AARGD-21-850835 to PWP).

**POSTER # 139**

**CAUSAL RELATIONSHIP BETWEEN SLEEP DURATION AND ALZHEIMER'S DISEASE: INSIGHTS FROM MENDELIAN RANDOMIZATION AND LATENT CAUSAL VARIABLE ANALYSIS**. Song S, Huentelman MJ, Piras IS. Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: The identification of modifiable risk factors, including lifestyle-related habits, offers opportunities for disease risk reduction or prevention. Sleep disturbances, such as insomnia, sleep apnea, and restless leg syndrome, encompass a wide category of conditions that affect sleep. Several studies have linked sleep disturbances with an increased risk of Alzheimer's Disease (AD).

Methods: To explore the causal relationship between sleep disturbances and AD risk, we conducted mendelian randomization (MR) and latent causal variable (LCV) analysis using sleep duration (SD) as the exposure and AD as the outcome. We leveraged publicly available Genome-wide Association Studies (GWAS) summary statistics from self-reported and accelerometer-derived SD from the UK Biobank (PMIDs: 30846698, 30952852) and six AD GWAS. We ran LCV analysis as a discovery analysis using three AD GWAS as exposure (GCST90012877, GCST007320, and GCST90027158), and then focused on the significant phenotypes for the MR analysis, using the same sleep GWAS and also three additional AD GWAS (PMIDs: 2416273, 24162737, 30820047). Inverse Weighted Variance (IWV) was employed as our primary analysis, and subsequently we used MR-Egger and Weighted Median methods. We tested for heterogeneity using the Cochran Q test.

Results: LCV analysis revealed a significant association of self-reported long sleep (gcp = -0.644; p = 2.04E-13) and accelerometer-derived sleep duration standard deviation (gcp = -0.507; p = 0.031). We focused on these phenotypes in the MR study, but did not validate the results using the same three AD GWAS. However, we replicated the results on one of the three other GWAS (β = -22.4; p = 4.9E-09). The results were not significant when we used MR-egger (β = -18.5; p = 0.260) and Weighted Median methods (β = -21.0; p = 0.518). Three SNPs were responsible for the signals (rs4577128, rs4727449, and rs79456170; p < 0.001), located in PRKCA, STAG3, and COMETT genes.

Conclusions: Our results do not suggest clear evidence of a causal association between SD and AD. Although the results were highly significant with two different methods in two independent GWAS, we failed to find consistency across the different datasets. Other studies failed to detect evidence of causal association between SD and AD by MR (PMIDs: 35918656 and 33150399). However, a recent study (PMID: 38301285) using the English Longitudinal Study of Ageing, was able to identify increased risk of dementia and AD associated with long sleep. The risk of AD associated with SD might be potentially independent from genetic factors but mediated by other processes such as astrocyte and microglia dysregulations (PMIDs: 35755779, 29563238).

**POSTER # 140**

**ABSENCE OF FMRI REPETITION SUPPRESSION FOLLOWING PERSPECTIVE SHIFTS MAY CONTRIBUTE TO AGE-RELATED SPATIAL MEMORY DEFICITS**. Srokova S, Barnes CA, Ekstrom AD. University of Arizona; Arizona Alzheimer's Consortium.

Background: An important facet of spatial memory function is the ability to remember places across different perspectives. Prior evidence suggests that older adults may show declines in spatial memory relative to younger adults, although whether perspective switching may be driving some of these differences remains unclear.

Methods: In the present study, a preliminary sample of young and older participants underwent fMRI as they completed a task tapping on spatial memory abilities across repeated or rotated perspectives. During encoding, participants viewed a series of virtual rooms containing trial-unique sets of five objects placed in random locations within the scene. After a 7 second delay, the room was viewed again, either from the same or rotated (50-degree) perspective. Participants indicated whether one of the five objects had moved to a new location. In our preliminary sample, older adults' spatial memory performance was worse than younger adults across both the same and rotated perspectives. We performed preliminary fMRI analyses to examine the neural correlates of perspective shifts, with the parahippocampal cortex (PHC) and hippocampus (HC) as two areas of interest. The present analyses focused on repetition suppression (RS) effects, a phenomenon believed to index the extent to which a given brain region represents a set of two stimuli as same or different.

Results: Whole-brain univariate analyses revealed evidence for RS in both younger and older adults across the PHC and HC, such that repeated presentation of the same perspective resulted in reduced fMRI BOLD relative to the first presentation. RS effects for the rotated perspective were observed in the HC but not in the PHC, indicating that spatial representations are perspective-independent in the HC but perspective-specific in the PHC. Separate statistical maps contrasting younger and older adults revealed no age differences in RS during repeated perspectives. However, rotated perspectives exhibited significantly greater RS in younger than older adults in the anterior hippocampus. Motivated by this finding, we extracted trial-wise parameter estimates from the anterior hippocampus. In younger adults, hippocampal estimates of hemodynamic response were significantly above baseline during first stimulus presentation, followed by a robust below-baseline deflection during the second presentation. This decline in fMRI BOLD was greatest in response to rotated perspectives. Additionally, generalized linear mixed effects modeling revealed that greater below-baseline 'deactivation' of the anterior hippocampus was associated with greater probability of correct memory judgements. In older adults, however, hippocampal response was not modulated by presentation order (first or second), perspective conditions (same or rotated), or memory success.

Conclusions: This age-related absence in RS for novel perspectives may point to the possibility that perspective-independent (allocentric) spatial representations in the hippocampus are less differentiated in older age. Therefore, the present data point to a potential neural mechanism that may contribute to impaired spatial memory in older adults.

**POSTER # 141**

**INJURY-INDUCED AUTOANTIBODIES AS BIOMARKERS FOR ALZHEIMER'S DISEASE.**
Stabenfeldt SE, Willingham C, Flores Prieto D, Diehnelt C. Arizona State University; Robust Diagnostics, LLC; Arizona Alzheimer's Consortium.

Background: An increased risk for Alzheimer's disease (AD) and neurodegenerative disorders (NDs) following a documented traumatic brain injury (TBI) has been identified in the clinic and AD-like pathology has been observed in preclinical TBI models. Studies of military personnel have identified TBIs as an independent risk factor associated with an up 60% increased risk of developing dementia. Commonalities exist between TBI and AD/NDs pathologies, yet, the direct connection and potential contribution of TBI to AD/NDs pathologies remains elusive. Therefore, understanding and elucidating the potential role of TBI-induced neurodegeneration would afford an opportunity to detect, prevent, and intervene early. Detection of those with high risk for developing AD/ND is critical. Post-TBI, a subset of patients experience persistent, chronic dysfunction and develop chronic AD/ND. An evaluation of these patients' autoantibody (aAb) profiles revealed elevated levels compared to healthy controls. Studies have shown also that a TBI event may induce increases in polyreactive IgM and class switching to IgG occurs for specific antigens. Prior has focused on evaluating general aAb profiles, yet the whole antigen immunoassays do not resolve epitope differences between patients. Measuring antibodies against specific epitopes can resolve reactivity differences between patients that whole antigen immunoassays cannot.

Methods: We developed and validated a microarray platform to assess the autoantibody (aAb) profile of key TBI biomarkers (GFAP, NFL, and MBP). We designed an antigen panel for GFAP, NFL, MOG, PLP1 and MBP then validated panel of markers using a pre-clinical mouse model of TBI (controlled cortical impact). This platform has high potential for translation as it only requires a small drop of blood for each microarray panel (<5uL). Blood samples were collected from a longitudinal cohort of mice over 1 month post-injury.

Results: We designed and fabricated the aAb microarray composed of peptide regions from reported or likely aAb epitopes from multiple neurological protein targets (e.g., GFAP, NFL, MOG, PLP1, MBP, TDP-43). The array also included control peptides from human immunodominant epitopes from Epstein-Barr Virus (EBV), Cytomegalovirus (CMV), Herpes Simplex Virus-1 (HSV-1), and Herpes Simplex Virus-2 (HSV-2) to demonstrate species specificity for the mouse samples. A total of 60 different peptide epitopes were generated per microarray. We successfully completed a one-month mouse study to collect longitudinal blood spot samples after the controlled cortical impact (CCI). A total of 24 mice were used in the study with n = 6 per sex and naïve and injured groups. The dried blood spot samples from the day 28 post-injury were first measured for both IgG and IgM binding for each peptide on the microarray. The results indicated a number of significantly different IgM responses ($p<0.05$) across multiple neurological epitopes, particularly NfL and PLP peptides.

Conclusions: We successfully designed and provided initial evidence that this aAb microarray can provide unprecedented profiling of TBI and neurodegenerative aAb epitopes. This tool provides insight into disease progression and neurodegenerative processes.

**POSTER # 142**

**THE TOPOLOGICAL LANDSCAPE OF PROTEINS ASSOCIATED WITH NEURODEGENERATIVE DISEASE.** Sugiyama M, Kosik KS, Panagiotou E. University of Tennessee at Chattanooga; University of California, Santa Barbara; Arizona State University; Arizona Alzheimer's Consortium.

Background: Neurodegenerative diseases, like Alzheimer's, are associated with the presence of neurofibrillary lesions formed by tau protein filaments in the cerebral cortex. While it is known that different morphologies of tau filaments characterize different neurodegenerative diseases, there are few metrics of global and local structure complexity that enable to quantify their structural diversity rigorously.

Methods: We employ for the first time mathematical topology and geometry (in particular, the Gauss linking integral, writhe and second Vassiliev measure) to classify neurodegenerative diseases by using cryo-electron microscopy structures of tau filaments that are available in the Protein Data Bank (PDB).

Results: This enables to achieve a consistent, but more refined classification of tauopathies, than what was previously observed through visual inspection. Progressive supranuclear palsy (PSP) is identified as an outlier, with a relatively more complex structure, reflected by a very small, but observable knotoid structure (a diagrammatic structure representing non-trivial global topology), which may be associated with pathological features, such as the presence of tufted astrocytes. Our results show that mathematical topology/geometry of cryo-EM structures alone identifies the PGGG motifs and the PHF6 and PHF6* motifs as sites of interest, which are known to regulate the aggregation capacity of tau protein experimentally. In addition, our results show a geometrical hierarchy of the PGGG motifs that differs for the 3R, 3R+4R and 4R tauopathies. We also employ the local topological free energy (LTE), a method of characterizing the topology of tau filaments relative to the topology of the folded state ensemble of proteins in the PDB by analyzing a culled data set of more than 13K proteins. Our results show that progressive supranuclear palsy (PSP) is the only tauopathy (along with the similar GGT) with a high LTE conformation at residues 302 - 305, which is in the vicinity of the 301 site, where mutations have shown experimentally to promote aggregation. By comparing R2 repeats of misfolded tau proteins with tau protein bound to microtubules and filamentous actin, we find that structures of misfolded tau R2 repeats are locally more stable and points to binding being associated with higher LTE values. We analyze the LTE of all known tau protein antibodies that are known to bind to tau filaments. Our results demonstrate that binding occurs with higher probability at the high LTE sites of an antibody. This may point to a method of predicting sites of binding for possible tau antibodies that could be used as a screening method for antibody selection.

Conclusions: Overall, our analysis reveals that topological metrics of structure capture novel, previously unknown aspects of their structure that can help classify them and point to specific patterns and sites of interest. This new mathematical framework for studying tauopathies could be helpful in quantifying aspects of their topological landscape that lead to aggregation, as well as to predict site specific methods of intervention.

**POSTER # 143**

**CAN TREATMENT OF INSOMNIA REDUCE PRECLINICAL BIOMARKERS OF ALZHEIMER'S DISEASE?** Taylor DJ, Huskey A, Emert SE, Nagy SM, Leete J, Kim K, Lopez N, Olson E, Grilli M, Kilgore S. University of Arizona.

Background: Insomnia is the most common sleep disorder, with 6-10% meeting criteria for chronic insomnia disorder. The risk of insomnia increases with age, and rates are twice as high in women as in men. Chronic insomnia is a risk factor for faster genetic and brain aging, and worse neuroimaging and neuropsychological markers of brain health. Two recent systematic and meta-analytic reviews also found that insomnia is a significant risk factor for neurodegenerative diseases such as dementia. One of the cohort studies found that not only was insomnia a significant risk for dementia, but the use of hypnotics to treat insomnia more than doubled the risk of developing dementia.

To date, no study has investigated if treating insomnia can reduce the risk of developing neurodegenerative disorders such as Alzheimer's, nor have the investigated potential mechanisms of action (e.g., reduction of neurodegeneration biomarkers). Cognitive Behavioral Therapy for Insomnia (CBTi) is considered the gold-standard, first line treatment of insomnia. The proposed study aims to determine if CBTi can reduce the risk of Alzheimer's Disease through the reduction of preclinical neurodegenerative biomarkers (e.g., GFAP, NFL, tau, and UCH-L1) and to examine potential mechanisms of change (e.g., improvement in REM and SWS).

Methods: Two-arm randomized design examined the efficacy of CBTi compared to a waitlist control (WLC) group in an unbalanced 9:1 ratio, to improve power to find within group effects, while also allowing for pilot between group effects. Participants were all aged 50-65 with complaints of insomnia. This age range was chosen because this is typically the earliest the neurodegenerative biomarkers (e.g., tau) first begin to express and thus be possible to see changes in after treatment. All study procedures are approved and monitored by the university's Institutional Review Board.

Neurodegenerative biomarkers (Primary outcomes for current proposal). Plasma aliquots will be used to assay neurodegenerative markers via Quanterix's Simoa Accelerator Laboratory, which is equipped to run ultrasensitive biomarker assays. The following neurodegenerative markers will be measured: glial fibrillary acidic protein (GFAP), tau, neurofilament light chain (NFL), and ubiquitin C-terminal hydrolase L1 (UCH-L1). We also banked PAXgene DNA and RNA samples and enough blood to examine other blood-based biomarkers: health (e.g., complete blood count, CHEM-20 panel, thyroid stimulating hormone), inflammatory (e.g., interleukin (IL)-6, IL-10, tumor necrosis factor-α), neurodegenerative (e.g., Amyloid-β, pTau-217) and aging (e.g., telomere length). Additional biomarker assays were beyond the budget of the current project.

Results: Self-report and objective assessments of sleep and mental health are pending completion of the trial, expected 8/29/24. Preliminary outcomes will be presented at the conference. Biomarker analyses will be conducted during that same time window, but unlikely available by the conference.

Conclusions: As indicated above, we have almost complete assessment in the current trial. The plan had been to bank the blood and perform assays as new funding came available. We received an AAC grant perform the neurodegenerative assays. We will then write up the results for both publication (expected submission 12/2024) as well as for preliminary data for an NIH R01 (expected submission 6/2025) for a fully powered study.

**POSTER # 144**

**BRAIN HEALTH LOTERÍA.** Teposte M, Pazzi M, Martínez L, Nava-Cabrales A, Hernandez M, Diaz C. Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: The prevalence of cognitive decline and neurodegenerative diseases such as Alzheimer's disease is increasing globally. Preventative strategies, particularly those focusing on lifestyle modifications and cognitive engagement, are crucial in mitigating the risks associated with these conditions. Traditional games and cultural activities offer a unique opportunity to engage diverse populations in cognitive exercises. Lotería, a traditional Mexican game similar to Bingo, is widely recognized and enjoyed within Hispanic communities. This project explores the creation of a brain health-themed Lotería game utilizing OpenAI's generative models to design educational and engaging content aimed at promoting cognitive health.

Methods: The development of the brain health Lotería game involved several stages: conceptualization, design, content creation, and evaluation. 144ognitive, a comprehensive literature review identified key brain health concepts and activities beneficial for 144ognitive stimulation. The conceptual framework for the game was then established, aligning traditional Lotería gameplay with educational objectives related to brain health.

OpenAI's design models were utilized to generate illustrations for the game cards. Specific prompts were designed to ensure that the generated content was accurate, culturally relevant, and engaging. A multidisciplinary team of healthcare professionals reviewed and refined the generated content to ensure scientific accuracy and cultural appropriateness.

Results: The development phase resulted in the creation of 16 individual Lotería cards, each uniquely designed with phrases that describe a specific brain health topic. These topics were selected based on their relevance to cognitive health and their potential to stimulate educational conversations. The phrases on the cards cover a range of subjects, such as healthy eating for brain health, sleep, physical activity, and social engagement.

Although the game has not yet been introduced to the community or shared with the general public, creating these 16 cards represents a significant step towards providing the Hispanic community with a novel and culturally resonant tool for cognitive engagement. By integrating traditional elements of Lotería with educational content on brain health, the game aims to foster cognitive exercises in an enjoyable and familiar format. This initial set of cards lays the foundation for a full-scale game that can be used in the community to promote cognitive health through interactive and culturally tailored activities.

Conclusions: The creation of a brain health loteria game using OpenAI demonstrates a promising approach to engaging diverse populations in cognitive health activities. The integration of traditional cultural elements with scientifically grounded content can enhance the accessibility and effectiveness of health education interventions. This project highlights the potential of leveraging AI technologies to develop innovative health promotion tools tailored to specific cultural contexts. Further development could incorporate more interactive and personalized elements, enhancing the game's effectiveness and appeal. This brain health lotería game represents a novel intersection of cultural tradition, health education, and advanced AI technologies, offering valuable insights into the development of culturally competent health promotion strategies.

**POSTER # 145**

**VALIDATING THE EFFICACY OF A NOVEL POTENT DYRK1A INHIBITOR (DYR533) IN THE TS65DN MOUSE MODEL OF DOWN SYNDROME.** Turk J, Winslow W, Tallino S, Judd J, Bartholomew SK, Mistry F, Hulme C, Dunckley T, Velazquez R. Arizona State University; University of Arizona; Arizona Alzheimer's Consortium.

Background: Most individuals with Down Syndrome (DS) develop Alzheimer's Disease (AD) pathology including amyloid beta (Aβ) plaques and neurofibrillary tangles by the fifth decade of life. Several proteins implicated in AD pathology have triplicated genes in DS, including dual-specificity tyrosine phosphorylation-regulated kinase-1a (Dyrk1a). Dyrk1a phosphorylates both the amyloid precursor and tau protein and has been shown to be upregulated in postmortem brain tissue of patients with DS and AD, rendering this protein an attractive therapeutic target to reduce hallmark AD pathogenesis. Our work has shown that a novel Dyrk1a inhibitor, termed DYR533, reduces Aβ and tau pathogenesis in the 3xTg-AD and PS19 mouse models. Whether DYR533 reduces AD-like pathogenesis in an animal model of DS remains to be known.

Methods: Here, we evaluated DYR533 in the Ts65Dn mouse model of DS. Starting at 4.5 months of age, disomic (2N) and trisomic (3N) Ts65Dn mice received daily intraperitoneal injections of either 0.625-, 2.5- or 10- mg/kg DYR533 or a vehicle control for approximately 3.5 months. Silmitasertib, a commercially available Dyrk1a inhibitor, was also included at a dosage of 25mg/kg to serve as a comparison. Mice underwent behavioral testing including rotarod (to assess motor function), elevated plus maze (epm; to assess anxiety-like behavior), and radial arm water maze (rawm; to assess spatial learning and memory) at 7 months of age, when soluble Aβ40 and 42 and phosphorylated pathological tau are present in the basal forebrain (Bf) and hippocampus (Hp) in 3N mice. At 8 months, mice were euthanized and the Bf and Hp were harvested.

Results: Behavioral analysis showed no significant difference between 2N vehicle control and 3N vehicle and dosed mice in the rotarod and epm tasks. In the rawm, 2N vehicle mice performed significantly better than 3N vehicle mice on Day 2-5 as evident by increased successful trials to find the hidden platform, and 3N 0.625mg/kg mice performed significantly better than 3N vehicle mice. Enzyme-linked immunoassays of the soluble fractions of Bf and Hp protein homogenates showed that treatment with DYR533 reduced Dyrk1a, soluble Aβ40 and Aβ42 as well as phosphorylated tau threonine 181.

Conclusions: Collectively, we demonstrate that DYR533 reduces Dyrk1a protein levels and AD-like pathogenesis in the DS Ts65Dn mouse model, setting the stage for further development of DYR533 as a potential therapeutic for DS with AD.

**POSTER # 146**

**COMBINING SPEAK OUT!® THERAPY PROGRAM WITH THE COMPUTER ASSISTED REHABILITATION ENVIRONMENT (CAREN) TO IMPROVE SPEECH INTELLIGIBILITY AND GAIT IN PATIENT'S WITH PARKINSON'S DISEASE: A CASE STUDY.** Wash EW, Lamb MA, Manriquez, A, Delap CM. Midwestern University.

Background: Parkinson's disease (PD) is a neurodegenerative disease that affects motor functions including speech, balance and ambulation. Due to the progressive nature of the disease, most patients with PD (PwPD) will eventually require therapeutic intervention with speech-language pathologists (SLP) and physical therapists (PT). These therapies are frequently provided separately with the aim of restoring and preserving function in speech intelligibility and movement. In contrast, studies have shown positive therapeutic outcomes with a multidisciplinary therapy team approach to the treatment and management of PD symptoms. Furthermore, studies have shown the overall benefit of regular intensive exercise routines for PwPD indicating that incorporating more movement during SLP sessions could improve a patient's speech intelligibility. The purpose of this study was to investigate the effectiveness of the SPEAK OUT!® program in combination with PT to improve speech intelligibility for PwPD using a multidisciplinary approach with the Computer Assisted Rehabilitation Environment (CAREN).

Methods: One participant with a diagnosis of PD and hypokinetic dysarthria was selected to complete the modified SPEAK OUT® program over the course of four weeks. SLP therapy sessions were held three times a week for a total of 12 sessions. The first and final week of therapy was held in a traditional clinical setting which consisted of administering the SPEAK OUT® program in a treatment room with the participant sitting at a table. Week two and three of the SPEAK OUT!® program were held on the CAREN using the same therapy tasks from week one. Decibel (dB) levels were used to measure vocal loudness which, if too low, can negatively impact speech intelligibility in people with PD. Decibel (dB) levels were recorded for all SPEAK OUT® tasks: pre-session conversation, vocal warm-ups, counting, reading, cognitive tasks and post-session conversation. Differences in participant's dB levels during pre/post session conversations were examined on a weekly basis. Data collected during weeks of traditional SLP treatment were then compared to data collected during weeks using the CAREN to assess differences in weekly dB gains across the two treatment settings.

Results: This study showed a 92% increase in average vocal amplitude during therapy weeks using the CAREN at 9.7 dB vs. average vocal amplitude recorded during traditional treatment setting at 5.05 dB. PT balance and gait improvements included decreased level of assistive device required from motorized scooter to walking sticks.

Conclusions: The results of this study are significant as they highlight weekly dB gains of over 90% during treatment weeks using the CAREN with walking as compared to dB gains where therapy was administered in a traditional SLP setting. Further research is required to determine the full therapeutic effects on speech intelligibility in PwPD when implementing aerobic exercise during SLP therapy as well as long term carry over effects. Additional discussion is warranted on how to effectively implement multidisciplinary therapy approaches to PD in a clinical setting.

**POSTER # 147**

**PROGRANULIN LEVELS AND LYSOSOMAL FUNCTION ALTER PRO-INFLAMMATORY CYTOKINE PRODUCTION BY MICROGLIA.** Yang AZ, Lin J, Harrison AM, Uppalapati CK, Maqsood S, Biparva P, Leyva KJ, Hull EE. Midwestern University; Arizona Alzheimer's Consortium.

Background: Progranulin (PGRN) deficiency and lysosomal dysfunction have been independently linked to neuroinflammation in Alzheimer's disease. PGRN is a pleiotropic signaling molecule whose activity depends upon differential proteolytic processing, where different PGRN products generated during this processing regulate inflammation, lysosomal function, and/or growth. PGRN and lysosome function are linked as the lysosome is a site of PGRN processing and the resulting PGRN subunits promote the function of several lysosomal proteases. In addition, in models of PGRN insufficiency, increasing the levels of PGRN restores lysosomal function and reduces inflammation. As the microglial-mediated inflammatory response is key to the development of neurodegenerative diseases, this work investigates the link between lysosomal function, PGRN, and inflammation. We hypothesize that the ability of PGRN to restore lysosomal function and reduce pro-inflammatory cytokine production depends upon appropriate processing and that PGRN may exacerbate an established inflammatory response. Thus, delineation of PGRN production and processing is key to determining biological effects of PGRN and the development of a future therapeutic.

Methods: The HMC3 human microglial cell line and primary mouse microglial cells were used to measure microglial activation and cytokine production by qPCR, immunomicroscopy, and flow cytometry.

Results: Results demonstrate that lysosomal function and proinflammatory cytokine production are linked in that disruption in lysosomal function increases microglial pro-inflammatory cytokine secretion, and proinflammatory conditions result in abnormal alkalization of lysosomes. Interestingly, supplementation with PGRN may decrease pro-inflammatory polarization of resting microglial cells but intensify an on-going pro-inflammatory response. Interestingly, dysfunctional lysosomes appear to have increased levels of complosome proteins, suggesting that lysosomal function may be linked at multiple levels to the inflammatory response.

Conclusions: As mutations in the gene encoding PGRN are implicated in both a dysfunctional lysosomal pH and in several neurodegenerative diseases, these results may provide a novel approach to regulate neuroinflammation, which may ultimately slow or prevent the development of disease.

**POSTER # 148**

**ASYMPTOMATIC EXTRACRANIAL CAROTID ATHEROSCLEROSIS IS ASSOCIATED WITH POORER COGNITIVE FUNCTION AND REDUCTIONS IN WHITE MATTER VOLUME AND PERFUSION.** Zahra S, French SR, Arias JC, Khakwani KZR, Escareno CE, Heitkamp EN, Wiskoski HE, Vazquez F, Ally M, Pugazhendhi A, Culwell GC, Vitali F, Bedrick EJ, Trouard TP, Alexander GE, Weinkauf CC. University of Arizona; Arizona Alzheimer's Consortium.

Background: There is increasing evidence that carotid stenosis is associated with cognitive impairment and dementia. But little is known about the associated changes in the brain. Although the brain has robust collateral blood flow and perfusion regulation, a potential mechanism for how carotid stenosis could result in cognitive decline is through chronic brain hypoperfusion. In the brain, white matter more than gray matter is susceptible to the vascular damage induced by chronic hypoperfusion. We investigated whether asymptomatic extracranial atherosclerotic disease (aECAD) is associated with cognitive impairment and whether that impairment is linked to white matter changes including hypoperfusion and volume loss.

Methods: A total of 150 study participants with a diagnosis of aECAD and/or ≥2 cardiovascular risk factors between the ages of 50-85 years were recruited from vascular clinics in Tucson, AZ. Participants underwent MRI scans to evaluate carotid stenosis percentage, brain volumes, and cerebral perfusion. Brain volumes were adjusted for total intracranial volume (TIV) prior to analysis. Pseudo-continuous Arterial Spin Labelling (pcASL) was used to measure perfusion signals. ASL images were analyzed using BASIL toolbox available in FMRIB Software Library (FSL). Each participant also underwent a neurocognitive testing battery. Spearman-rank correlation was used to assess the association between the continuous variables. Cognitive status among perfusion groups was compared using Wilcoxon rank sum test. Linear regression was used to control for potential confounders.

Results: Wechsler Adult Intelligence Scale (WAIS) Coding, WAIS Symbol Search, and the Stroop Color-Word test, which assess processing speed and executive function, were negatively correlated with carotid stenosis ($p<0.01$). Degree of carotid stenosis was inversely associated with white matter perfusion ($r= -0.32$, $p<0.01$) and white matter volume ($r=-0.28$, $p<0.01$). The decrease in perfusion was consistent even after adjusting for age, sex, cardiovascular risk factors and white matter lesion volumes. ($\beta$ coefficient= -0.27, $p= 0.03$). The group with low-perfusion had lower WAIS Coding scores compared to the high-perfusion group ($p=0.05$), while other cognitive tests (WAIS Symbol Search, Stroop Color-Word test) did not differ significantly.

Conclusions: Asymptomatic extracranial atherosclerotic disease is associated with poorer cognition, white matter hypoperfusion and white matter volume reduction. Still more, in a small subset of participants (n=15), we found that surgical treatment significantly increased perfusion compared to baseline. Understanding mechanisms of cognitive dysfunction associated with aECAD will build impetus for more targeted treatments in this population that currently is not clinically evaluated or treated for cognitive outcomes.

**POSTER # 149**

**ADVANCING NUTRIENT DELIVERY IN STRETCHABLE MICROFLUIDIC DEVICES FOR NOVEL ALZHEIMER'S IN-VITRO ANALYSIS.** Bradbeer M, Graudejus O, Rowan C, Wong RP, Wood L, Holberton A. BMSEED; Georgia Tech; Arizona State University.

Background: Accurate in-vitro models are essential for preclinical drug screening for Alzheimer's disease (AD) and Alzheimer's related dementias (AD/ADRD) as almost all clinical trials for AD drugs have failed due to inadequate cell culture and animal models. BMSEED aims to develop an in-vitro model of AD that more accurately represents the bioelectrical and biomechanical in-vivo environment by merging a novel microfluidic cell culture platform with integrated stretchable microelectrodes. The AD model is made of a stretchable elastomer and includes two chambers separated by a microfluidic channel to perfuse cells with drugs/nutrients and assess crosstalk between different cell types. In Phase I of the Fast Track NIH grant, we demonstrated feasibility of culturing primary mouse neurons, astrocytes, and microglia in stretchable AD devices and that device integrity is maintained (both mechanical and electrical) after stretching. Current Phase I tests focus on optimizing culture conditions for hiPSC-derived cells, ensuring efficient nutrient delivery through the microfluidic channel into both chambers. Entrapped air during gelatin injection of the cell chambers can block channel exits and electrode recording sites, impeding the diffusion of nutrients. This project explores if plasma treating devices to increase hydrophilicity before gelatin injection has any effect on the formation of bubbles or the diffusive characteristics of the device.

Methods: Prolonged passive diffusion and active perfusion tests were conducted on 3 stretchable and 3 non-stretchable devices, collecting diffusive data over 24 hours. Samples were plasma treated in two sample groups (Level 2 [~80W] for 2:15min and Level 3 [~120W] for 1:15min) before gelatin injection and incubated at RT for 2 hours before testing. In addition, flowrate data of the injection medium through the microfluidic channel before and after stretching at 50% was collected for 4 stretchable devices, 2 in each plasma condition sample group.

Results: Plasma treatment effectively eliminated gelatin bubbles in non-stretchable devices with little to no change in diffusive speed, efficacy, or quality between plasma conditions. In stretchable devices, higher plasma treatment level resulted in an 80% decrease in entrapped gelatin bubbles over recording sites in the cell chamber and a higher diffusive efficacy than lower treatment levels at the same timepoints. Overall, active perfusion resulted in faster and more consistent diffusion through entire device than passive testing in both sample groups. Additionally, mean differences in flowrate before and after stretching were below 0.5uL/min and within the error margin for both plasma conditions. Statistical testing confirms flowrates before and after stretching are not significantly different, which is consistent with prior control testing, and that device integrity was maintained through plasma treatment.

Conclusion: Plasma treatment is effective in increasing hydrophilicity and decreasing gelatin bubbles in microfluidic devices while maintaining device integrity. Current ongoing testing includes determining if the plasma energy level or length of treatment is more effective at reducing entrapped air and testing a PEI coating to further increase hydrophilicity and cell attachment. For ongoing Phase II testing, perfusion in addition to plasma treatment is recommended to increase diffusion efficiency and nutrient delivery to primary mouse cells in stretchable devices.

# Arizona Alzheimer's Consortium
# 25th Annual Scientific Conference

## Additional Abstracts

**SELF-REPORTED MODERATE TO VIGOROUS PHYSICAL ACTIVITY IS ASSOCIATED WITH REDUCED SUBJECTIVE COGNITIVE COMPLAINTS IN OLDER ADULTS**. Aboobucker S, Malek-Ahmadi M, Al-Jubouriy H, Shaikh F, Jooste C, Kuramoto A, Coon DW, Atri A. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: Past research supports the beneficial impact of regular physical activity on cognitive ability. However, a lack of studies exists on the association between an individual's regular physical activities and their subjective perception of cognitive decline. Here, we examine the relationship between different exercise intensities (light/sedentary, moderate, and vigorous) and participant ratings of their abilities in various domains (Memory, Language, Visuospatial, Executive - Planning, Executive – Organization, and Executive - Divided Attention) of the Everyday Cognition (ECog) survey.

Methods: The Center for Healthy Aging's Longevity Study: Learning From Our Elders at Banner Sun Health Research Institute is a longitudinal study that examines various contributors of healthy aging among older adults in Arizona. During their annual interviews, 130 healthy older participants with either normal cognition or mild cognitive impairment were administered the Rapid Assessment of Physical Activity (RAPA). They were subsequently stratified into light/sedentary, moderate, and vigorous exercise categories based on their responses. Participants also submitted responses to a 39-item Everyday Cognition (E-Cog) questionnaire, in which individuals report whether their ability to perform everyday tasks has changed compared to a decade ago. Kruskal Wallis and robust regression statistical tests were utilized to analyze the data.

Results: Among the 130 participants, 71.5% were female. The mean age was 80.8 years old (± 7.9 years). The median age of participants was 81.0 years (± 9.8 years), and their mean education level was 15.6 years (± 1.4 years). The mean scores were 26.6± 3.1 and 29.0±1.3 on the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE), respectively. Kruskal Wallis analyses demonstrated statistically significant differences between the physical activity levels on the Memory ($p=0.04$), Language ($p=0.04$), Executive-Organization ($p=0.003$), and Executive-Divided Attention ($p=0.04$) domains of the E-Cog. However, after adjusting for age, sex, and education level a statistically significant relationship between physical activity level and Executive-Organization remained. Those with moderate and vigorous activity levels reported significantly lower frequencies of subjective cognitive complaints in the Executive-Organization domain (both $p = 0.003$).

Conclusions: Our results suggest that moderate to vigorous physical activity is associated with reduced complaints of decline in executive function. These findings support the conclusions of other studies, which demonstrate that increased physical activity enhances the performance of older adults in executive function-related tasks.

**EARLY-STAGE PARTNERS IN CARE (EPIC) II: PRELIMINARY RESULTS FROM AN RCT.**
Glinka A, Carll P, Gonzalez-Pyles S, Perez S, Carbajal B, Cordova L, Coon DW. Arizona State University; Arizona Alzheimer's Consortium.

Background: There are 6.9 million people are living with Alzheimer's disease (AD) in the United States. Few evidence-based interventions have been identified to help people with early-stage ADRD (EPs) and their care partners (CPs) manage ongoing memory changes and associated distress and help them prepare for the future. The Early-Stage Partners in Care (EPIC) II study is a randomized clinical trial of a manualized psychoeducational skill-building and care planning intervention that targets the lack of evidence-based stage-appropriate interventions for these EP-CP dyads.

Methods: EPIC II randomly assigned groups of 6 to 8 dyads to either the EPIC II intervention or a Waitlist Comparison Group (WCG). The EPIC intervention was delivered initially face-to-face in Arizona and Nevada with co-leaders from ASU and the Desert Southwest Chapter of the Alzheimer's Association. However, the COVID-19 pandemic led to an initial shut-down of the study followed by a change to Zoom-based delivery that subsequently expanded the study's reach across the nation. The EPIC intervention lasts 7 weeks and consists of 6 weekly group sessions of 2.5 hours each and one individualized 90-minute session. EPIC creates a supportive environment that provides education on memory changes associated with ADRD; develops mood management, communication, and stress reduction skills; helps clarify the EP's care values and preferences for future care tasks; and develops an individualized plan for the future. Within two weeks prior and post EPIC or WCG assignment, EPs and CPs completed separate assessments using measures with established reliability and validity.

Results: Despite the pandemic, the study enrolled 139 dyads with 88.4% being spousal partners. EPs ranged in age from 39 to 92 (average 71 years); 61.6% were male; 92% self-identified as white; and 5.1% Latino or Hispanic; 90.6% were married or partnered; and, 63.1% college graduates. CPs ranged in age from 42 to 89 (average age 67 years); 64% female; 89.2% white and 8.6% Latino or Hispanic; 93.5% were married or partnered; and 79% college graduates. Challenges related to the recruitment of ethnic/racial minority early-stage participants were exacerbated due to the pandemic. Analyses are still underway but high proportions of EPs and CPs reported overall benefit from the intervention (97.7% of EPs and 100% of CPs). Over 93% of EPs and CPs said the EPIC intervention helped them better understand memory loss; increased their confidence in dealing with memory problems; and improved their partner's life. In all cases, CPs reported higher levels of perceived benefit than EPs with over 93% of CPs saying EPIC made their lives easier; enhanced their ability to care for themselves; enhanced their ability to care for their partner; and improved their own life. The proportion of EPs reporting benefit on these factors ranged from a low of 78.7% (enhanced their ability to care for themselves) to 89.6% (improved their own life). When compared with WCG participants, EPIC CPs showed reductions in depressive symptoms and loneliness as well as improvements in overall quality of life, positive interactions with their EP, and care preparedness. EPIC EPs also reported improvements such as reduction in relationship strain with their CP.

Conclusions: Initial findings from the EPIC II RCT demonstrated positive outcomes and perceptions of benefit when delivered in person as well as virtually. Additional analyses of pre-post outcomes as well as maintenance of gains are underway.

**SEX DIFFERENCES IN VERBAL MEMORY AND NEUROFIBRILLARY TANGLE BURDEN: FINDINGS FROM COGNITIVELY INTACT OLDER ADULTS AND CLINICOPATHOLOGICALLY CONFIRMED ALZHEIMER'S DISEASE**. Gomez A, Auman B, Arce R, Belden C, Beach T, Atri A. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium; Arizona State University.

Background: Females tend to score higher than males on neuropsychological measures of verbal memory yet have been shown to have greater neurofibrillary tangle pathology than males. This study aims to explore sex differences in verbal memory performance and tangle burden.

Methods: We compared 177 cases with Alzheimer's disease (AD) (82 male and 95 female) to 275 non-AD cases classified as cognitively normal (CN) (138 male and 137 female) from the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) and Brain and Body Donation Program (BBDP). Verbal memory was assessed using the Rey Auditory Verbal Learning Test (AVLT). Tau tangle density and Braak scores were measured through histological examination of autopsy tissue.

Results: In the CN group, there were significant small-to-medium positive relationships between sex and all measures of AVLT performance. CN females had significantly higher AVLT total learning scores, AVLT delayed recall scores, AVLT recognition hits, and memory efficiency scores than males. In AD, there was a significant medium positive relationship between sex and AVLT total only. AD females had significantly higher AVLT total learning scores than males, but no other significant sex differences in AVLT performance were found. In the CN group, there were significant small positive relationships between sex and all measures of tangle pathology. CN females had significantly higher entorhinal tangle density, hippocampal tangle density, total tangle density, and Braak scores than males. There were no significant sex differences in tangle pathology within the AD group. In the AD group, age at death and age at onset of dementia were significantly later in females compared to males. Sex was significantly correlated with age of dementia onset and age at death. Braak stage and years with dementia had small-to-medium significant negative relationships with memory efficiency scores. Both relationships were moderated by sex.

Conclusions: Consistent with prior research, our findings demonstrate sex differences in verbal memory and neurofibrillary tangle pathology. Females score higher on verbal memory tasks despite having more tau pathology in brain regions associated with verbal memory, which may suggest that females have greater cognitive reserve and resilience to brain aging and pathology. Females' age at onset of dementia is later than males, suggesting that higher neuropsychological test performance in females could mask AD pathology, in turn delaying diagnosis. Our results support the importance of implementing sex-adjusted neuropsychological norms into clinical practice to improve earlier diagnosis and treatment of dementia and AD in females.

**CAREPRO VIRTUAL: PILOT STUDIES WITH TWO DISTINCT SAMPLES.** Gonzalez-Pyles S, Carll P, Glinka A, Cordova L, Carbajal B, Pérez S, Cuc A, Locke D, Coon DW. Arizona State University; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Over 6.9 million people live with Alzheimer's disease and related dementias (ADRD) in the United States. Family caregiving for people with ADRD leads to a host of negative outcomes including poorer emotional well-being and physical health, and attenuating social support. These negative outcomes highlight the need for evidence-based programs to reduce distress and enhance emotional well-being, including programs that address barriers to caregiver participation including transportation challenges, caregiver chronic illness or functional impairments, and work schedules for employed caregivers. The COVID pandemic provided a unique opportunity to adapt a nationally recognized evidence-based caregiver intervention Care Partners Reaching Out (CarePRO) for Zoom-based delivery.

Methods: CarePRO Virtual is a skill-focused program conducted over 5 weeks via Zoom. Participants join the group sessions to learn how to apply different skills (relaxation, mood management, communication, and behavior management skills) and overcome daily stressors resulting from caring for loved ones with ADRD. Between sessions, a designated coach meets one-on-one with each participant for skill-reinforcement. The current study conducted two separate single arm pre-post preliminary trials—one for participants recruited from a health care system and another for participants recruited from the community at large. Outcomes were derived through individual assessments given pre- and post-intervention.

Results: Twenty-six self-identified caregivers participated in a CarePRO Virtual intervention pilot from the health care system and twenty-four from the community were part of another pilot. While the majority of caregivers in both groups were women (approximately 80%), backgrounds differed somewhat across the two groups. Those from the community were: younger (average age 63 vs. 71 years old); more ethnically diverse (72% NHW with 24% self-identifying as Latino/Hispanic vs. 88.5% NHW and 0% Latino/Hispanic); more often employed (40% vs. 14.3%); and less often spouses of the care recipient (68% vs. 92%). Caregivers in both settings reported reductions in target complaint stress as well as improvements in caregiver self-efficacy, leisure time satisfaction, and care preparation. However, there were some differences in positive outcomes: caregivers from the health system reported reductions in caregiver burden and increased social support satisfaction, whereas caregivers from the community reported reductions in depressive symptoms, negative coping, and worry. Regardless of recruitment source, 100% of caregivers reported overall benefit from CarePRO Virtual. Over 95% also said CarePRO enhanced their ability to provide care; increased their understanding of memory loss; increased their confidence in managing behavior problems; and, made their lives easier.

Conclusions: CarePRO Virtual was found to be a feasible and acceptable caregiver intervention. Findings from two pilot studies with distinct samples also showed CarePRO Virtual positively impacted key caregiver outcomes for its participants—albeit somewhat differently for the two samples. These results will help shape applications for future CarePRO Virtual intervention research including the potential to further tailor the program for different populations.

**LONGITUDINAL MODELING OF AMYLOID ACCUMULATION IN ALZHEIMER'S DISEASE USING PET IMAGING.** Guo Z, Li S, Wu T, Malek-Ahmadi M, Su Y. Binghamton University; Banner Alzheimer's Institute; Arizona State University.

Background: Alzheimer's disease (AD) biomarkers are crucial for diagnosis, prognosis, and aiding in clinical trials. There is substantial individual level variability in the disease onset and progression in relation to age making it challenging to develop population level disease progression models that can fit observed biomarker data at individual level. Recently a Sampled Iterative Local Approximation (SILA) algorithm was proposed that estimates individual onset age of biomarker positivity and predicts the temporal biomarker trajectory as a function of disease progression. In this study, we apply an improved version of the SILA model to the Alzheimer's Prevention Initiative-Autosomal Dominant Alzheimer's Disease (API-ADAD) cohort and the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset.

Methods: API-ADAD and ADNI florbetapir amyloid PET data was processed using standard in-house procedures and converted to the Centiloid scale. A systematic statistical approach to detect outliers and remove erroneous PET-based amyloid measurements was implemented. A logistic regression model was fitted to the API-ADAD dataset where ground truth amyloid status can be inferred from the PSEN1 mutation status and participants age to construct a probabilistic model of amyloid positivity based on global amyloid burden index. Subsequently, we employed the SILA model to estimate rate of amyloid change as a function of global amyloid burden, generate a non-parametric amyloid accumulation trajectory, and estimate individual amyloid positivity onset ages.

Results: It is evident that outlier rejection improved the fitting performance of the SILA model. The estimated amyloid onset ages for the mutation carriers of the API-ADAD cohort and the ADNI cohort are 32.65 years (standard deviation: 10.92) and 73.93 years (standard deviation: 13.41), respectively. In addition, the results indicated that although the ADAD mutation carriers had an earlier amyloid onset age, the rates of amyloid accumulation were slower for ADAD mutation carriers.

Conclusions: We successfully modeled the 30-year pattern of amyloid accumulation in AD using data from individuals at various Alzheimer's stages, estimated individual amyloid onset ages, and compared the results of two cohorts. This approach also allows studying other factors (such as sex, type of APOE carriers) associated with amyloid accumulation rates.

**MENOPAUSE VARIATIONS ON BRAIN FUNCTIONING: A FOCUS ON GENE EXPRESSION IN REPRODUCTIVE AND BRAIN TISSUES**. Plaisier S, Lizik C, Oyen E, Newbern J, Bimonte-Nelson H, Wilson MA. Arizona State University; Arizona Alzheimer's Consortium.

Background: In women, surgical menopause induced by ovary removal has been associated with cognitive decline and increases in dementia risk. In preclinical rodent models, it has been well-documented that surgical removal of ovaries via ovariectomy (Ovx) impacts learning and memory. In addition, we have recently shown that another type of surgical menopause, hysterectomy with ovarian conservation, impairs cognition in a rodent model. However, the molecular underpinnings of the impacts of surgical reproductive tract manipulations are poorly understood.

Methods: In this study, we use transcriptomics to identify hormone-uterus-brain-behavior relationships at the molecular level. To examine the gene expression profile with and without its primary hormonal stimulator, the ovaries, uterine and brain tissues were collected from an animal model with and without Ovx. RNA sequencing of the brain tissues was performed with four regions of the brain that are associated with learning and memory and are analogous to regions affected in Alzheimer's disease: frontal cortex, entorhinal cortex, dorsal hippocampus, and ventral hippocampus. We observed that gene expression profiles of the brain samples clustered by brain region; therefore, we conducted differential expression analysis between samples with and without removal of the ovaries in each brain region separately.

Results: RNA sequencing of the uterine tissues revealed broad scale changes in gene expression after Ovx. RNA sequencing of the brain regions showed subtle changes after Ovx compared to the uterus. The entorhinal cortex showed the largest number of differentially expressed genes, more than double the number found in the other regions assayed. Functional enrichment analysis to characterize these sets of differentially expressed genes and correlation with specific aspects of learning and memory are ongoing.

Conclusions: Collectively, this work shows how the uterus is impacted by removal of its primary hormonal stimulator, the ovaries, as well as how removal of the ovaries affects the central nervous system, together yielding insight into the molecular factors underlying changes in cognitive function with reproductive tract manipulation. The knowledge gained from this study will have profound impacts on deciphering hormone-uterus-brain-behavior relationships, and will directly address the gap in the field regarding molecular contributions to cognitive outcomes associated with varied experiences of menopause during aging.

**GETTING INTO DETAIL: CHARACTERIZING THE PERFORMANCE OF INDIVIDUALS WITH AMCI IN THE RAVLT.** Rodríguez Roldán CM, Auman B, Ho A, Tremblay C, Arce R, Belden C, Beach T, Atri A. Banner Sun Health Research Institute; Banner-ASU Neuroscience Scholars; Arizona Alzheimer's Consortium.

Background: Mild Cognitive Impairment (MCI) can be defined as not normal, not demented. It is subdivided into amnestic (aMCI) and non-amnestic (naMCI) types. aMCI is usually regarded as an early stage of pre-dementia Alzheimer's disease (AD). Previous research suggests that AD is characterized by impairment in encoding and retention. This study characterizes in detail the pattern of memory deficits seen in patients with aMCI in the Rey Auditory Verbal Learning Test (RAVLT).

Methods: Subjects included 76 patients with aMCI and age-matched controls (total N = 152) drawn from the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) and Brain and Body Donation Program (BBDP). The Memory Efficiency Index (MEI), created by Ricci et. al., was calculated for both groups. T-Tests were used to compare MEI scores, as well as RAVLT Total Learning (TL), Delayed Recall (DR), Recognition (RC), and False Positives (FP) raw scores. ROC Analysis was used to select a criterion for diagnosing aMCI. The control group was subdivided into age groups and means and SDs were calculated to derive internal normative data. Utilizing the control group data, the z score for each task was calculated for each individual. Then the following labels were assigned to each subject: Learning Failure (LF: TL z score < -1.3); Storage Failure (SF: DR z score < -1.3 and RC z score < -1.3); Retrieval Failure (RF: DR z score < -1.3 and RC z score > -1.3); and Discrimination Failure (DF: DR z score > -1.3 and RC z score < -1.3). Finally, a Fisher's Exact Test was run to compare the two groups in each variable.

Results: The aMCI group performed significantly poorer than the control group in all RAVLT tasks, with large effect sizes in TL ($p < .0001$, $d = 0.80$), DR ($p < .0001$, $d = 0.95$), and RC ($p < .0001$, $d = 0.90$), and a medium effect size in FP ($p = .0001$, $d = 0.66$). The aMCI group had a significantly lower MEI ($M=1.32$, $SD=0.60$) than the control group ($M=1.84$, $SD=0.31$), $p < .0001$ and $d = 1.09$, indicating a large effect size. The best criterium for distinguishing aMCI from controls was MEI ≤ 1.34, with 51% sensitivity and 93% specificity; and a PPV of 81%, and a NPV of 78%. When looking at specific memory stages, aMCI had greater rates of LF ($p < .0001$) and SF ($p < .0001$), while no significant difference was observed regarding RF ($p = .45$) and DF ($p = .79$). Finally, aMCI status was confirmed to have high cases with AD pathology at autopsy when compared to controls ($p = .0013$).

Conclusions: The MEI proves to be a useful measure to help differentiate aMCI from normal aging. Its high specificity, PPV, and NPV may be useful for the clinical setting, while its low sensitivity could be attributed to the very nature of this diagnostic entity, that presents with high variability. As expected, the aMCI group overall performance in the RAVLT was worse than the control group, yet the different stages of memory were not equally impaired, with learning and storage being more significantly affected. This is the same tendency observed in AD dementia. Therefore, future research on aMCI should focus on these memory stages as measures of delayed recall alone may be less reliable.

**INFLUENCE OF EXERCISE AND GENISTEIN TO MITIGATE THE DELETERIOUS EFFECTS OF HIGH-FAT HIGH-SUGAR DIET ON ALZHEIMER'S DISEASE RELATED MARKERS IN MALE MICE.** Shah J, Orosz T, Singh A, Parameshwar SL, Gross R, Smith N, Vroegop S, Sudler S, Porter J, Colon M, Jun L, Babu JR, Shim M, Broderick TL, Al-Nakkash L. Midwestern University; Ponce Research Institute, Puerto Rico; Auburn University.

Background: The prevalence of obesity and related consequences including insulin resistance and Alzheimer's-like neuropathology has increased dramatically in the last decade. Contributing to this prevalence is the shift in the lifestyle preference away from wholesome foods and exercise to the Western-style diet and sedentarism. Despite advances in drug development, a healthy diet and regular exercise remain the most effective approaches to mitigating the unwanted sequelae of diet-induced obesity on brain health.

Methods: In this study, we used the high-fat high-sugar (HFHS) mouse model of neurodegeneration to examine the effects of exercise training (HFHS+Ex), genistein treatment (HFHS+Gen), and combination treatment (HFHS+Ex+Gen) on proteins relating to neurodegeneration in brain of male mice.

Results: After a period of 12 weeks, as expected, HFHS feeding increased body weight, adipose tissue weight, and systemic plasma inflammation (TNF-α) compared to lean mice, which were fed a standard diet. HFHS feeding also increased protein expression of brain markers of insulin resistance (pGSK-3β, p-IR), apoptosis (caspase 3), early neurofibrillary tangles (CP13), and amyloid-beta precursor (CT20). Compared to HFHS mice, Ex decreased body weight, plasma TNF-α, and the expression of pGSK-3β, caspase 3, CP13, amyloid-β precursor (22c11), and ADAM10. Treatment with Gen was equally protective on these markers and decreased the expression of p-IR. Combination treatment with Ex and Gen afforded the greatest overall benefits. Mice in this group exhibited the greatest reduction in body and adipose tissue weight and all brain markers, except for 22c11 and ADAM10, were decreased compared to mice fed a HFHS diet. In addition, levels of 4G8, which detects protein levels of amyloid-β, were decreased with combination treatment.

Conclusions: Our results indicate that exercise training, genistein supplementation, or combination treatment provide varying degrees of neuroprotection from HFHS feeding-induced Alzheimer's pathology.

**ASPIRIN AND METFORMIN IMPROVE COGNITIVE FUNCTION AND REDUCE CELLULAR SENESCENCE IN SENESCENCE ACCELERATED MOUSE-PRONE 8 (SAMP8) MICE.** Shelton W, Glamoc D, Yi-An C, Daoud L, Mody A, Broderick TL, Al-Nakkash L, Shim M. Midwestern University; Arizona Alzheimer's Consortium.

Background: Although the etiology of Alzheimer's disease (AD) is unknown, aging is the best-known risk factor for AD. Increasing evidence suggests that accumulation of senescent cells is a significant contributing factor to aging and/or age-related pathologies. Although senescent cells comprise only a small fraction of tissues, their presence can have a significantly negative impact on tissue homeostasis. Senescent cells secrete inflammatory cytokines and extracellular proteases, known as senescence-associated secretory phenotype (SASP). Studies have suggested that the accumulation of senescent cells in endocrine tissues may contribute to the development and/or progression of metabolic diseases. For example, insulin resistance is another risk factor for the development and progression of AD.

Methods: To test the hypothesis that age-related inflammation and insulin resistance play an important role in the pathogenesis of AD, we analyzed memory function and the level of senescence markers in aged (8-month-old) SAMP8 mice fed an aspirin- or metformin-containing diet for five months.

Results: Aged SAMP8 mice fed an aspirin- or metformin-containing diet exhibited improved glucose tolerance compared with mice fed a control diet. In addition, the Y-maze revealed that the percentage of alternation was increased in the aspirin- and metformin-fed groups, suggesting that these treatments improved short-term spatial memory. Moreover, long-term feeding with aspirin and metformin reduced the levels of senescence markers in the visceral adipose tissue.

Conclusions: Our study suggests that age-related inflammation and subsequent metabolic disturbances in the peripheral tissues may contribute to the development and progression of AD. Further characterization of other tissues is in progress.

**SINGLE-CELL IN SITU TRANSCRIPTOMICS AND PROTEOMICS REVEALS NEURAL CELL HETEROGENEITY AND INTERACTIONS IN HUMAN FFPE BRAIN TISSUES**. Wang Y, Ellison M, Guo J. Arizona State University; Arizona Alzheimer's Consortium.

Background: The various cell types in the brain cooperate collectively to achieve high-order mental functions. To accurately observe and precisely manipulate brain activities, it is required to have much greater knowledge of the molecular identities of specific cell types. This knowledge is also fundamental to the discovery of the cell-type targeted therapy to treat brain disorders. However, due to the technological limitations, it is currently unknown exactly how many cell types and subtypes exist in the brain.

Methods: To enable highly multiplexed single-cell in situ analysis, we have developed cleavable fluorescent probes (CFP) for comprehensive molecular profiling in single cells in situ. In this method, affinity probes, which can target biomolecules with high efficiency and specificity, are conjugated to fluorophores through a chemically cleavable linker. In the first analysis cycle, different probes labeled with varied fluorophores are applied to bind to their molecular targets in single cells. After fluorescence imaging and data storage, all the different fluorophores coupled to affinity probes in the whole specimen are efficiently cleaved simultaneously without loss of the integrity of any biomolecules. Upon continuous cycles of target binding, fluorescence imaging, and fluorophore cleavage, this approach enables the quantification of the identities, positions and abundances of a large number of different genomic loci, transcripts and proteins together in individual cells of intact tissues.

Results: We stained 12 different RNA cell markers to visualize varied cell types in the same human brain FFPE tissue. We also stained >35 proteins on 5 human hippocampus FFPE tissues. We classified the >1 million individual cells into different cell clusters and subclusters, based on their gene expression pattern.

Conclusions: We observed different hippocampus subregions are composed of cells from different clusters. And certain specific cell clusters are prone to associate with or avoid other specific cell clusters in the hippocampus.


# 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. 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 nine years (2015-2023). With Alzheimer's disease affecting roughly one in nine people 65 years old and over, and one in three people 85 years old and over, research on Alzheimer's disease (AD) and AD-related dementias (ADRD) exemplifies the types of endeavors that ASU seeks to promote, and a focus on innovative 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 Bimonte-Nelson) which help 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 their related collaborative discovery efforts that span molecular to behavioral outcomes in aging, AD, and ADRD. Research includes basic, translational, and clinical approaches to: advance understanding of molecular mechanisms by which a specific APOE gene variant mitigates AD onset and progression among African Americans to help in the development of targeted therapeutic interventions for this population (Brafman laboratory); test whether chronic unpredictable stressors exacerbate memory decline in female rats as they age (Conrad laboratory); examine specific AD-associated conformational variants of tau that play key toxic roles in the early stages of AD to discover promising therapeutic targets for treating AD (Sierks laboratory); determine whether tracking autoantibody profiles after traumatic brain injury provides prognostic and diagnostic insight into AD and other neurodegenerative pathology (Stabenfeldt laboratory); evaluate how neural complexity, such as dendritic structure and spine morphology, guides learning abilities in juvenile and middle-aged male and female mice to understand relationships and putative sex differences between cortical structure and cognition during aging (Verpeut laboratory); systematically determine the effects of menopause variants and clinically-used hormone therapies on the brain and cognition during aging (Bimonte-Nelson laboratory); study the molecular mechanisms underlying memory changes associated with surgical menopause (Wilson laboratory); develop better retinal imaging enhancement tools to assist in the study of AD and its progression (Wang laboratory); compare test-related stress levels between cognitive and motor tests shown to correlate with AD progression to improve primary care patients' willingness to be tested (Schaefer laboratory); evaluate the effects of an affordable Multi-Sensory Stimulation Environment (MSSE) on stress, depression, and agitation in patients with behavioral and psychological symptoms of dementia (Sharp laboratory); implement and evaluate a MCI and dementia screening and referral protocol as part of a shelter intake process for older adults experiencing homelessness (Ross laboratory); and assess the impact of a Zoom-based delivery skills training and care planning intervention to address the concerns of caregivers who have placed their loved ones with ADRD in long term care facilities (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 and

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 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 to advance the scientific study, treatment and prevention of Alzheimer's, Parkinson's, and other neurodegenerative diseases. The partnership includes the establishment of the Neurodegenerative Disease Research Center (1). The Center is an extension of the partners' work with the Arizona Alzheimer's Consortium and is envisioned to become one of the world's largest basic science centers for the study of Alzheimer's and other neurodegenerative diseases. The Center 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. The Center 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 Center 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 of engaging future scientists in aging and neurodegenerative research to yield maximal impacts on research discovery and translational outcomes. The ADRC Research Education Component, co-directed by Dr. Roberta Brinton (U of A) and Dr. Heather Bimonte-Nelson (ASU) 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

| Name (last, first) | Degree | Role on project |
|---|---|---|
| Abbas, Lori | | High School Student |
| Alrahyani, Mohammed | MS | Doctoral Student, Graduate Service Assistance |
| Andrew, Kieran | UG | Undergraduate Student |
| Anyigbo, Kamdikachukwu | UG | Undergraduate Student |
| Arellano, Antonio | UG | Undergraduate Student |
| Asadifar, Sadaf | UG | Undergraduate Student |
| Azizi, Ian | UG | Undergraduate Student |
| Badhwar, Neha | UG | Undergraduate Student |
| Baker, Lauren | MS | Research Technician |
| Baker, Lauren | MS | Research Technician |
| Balasubramanian, Kavya | BS | Graduate Student Researcher |
| Belgrave, Melita | PhD | Co-Investigator |
| Bimonte-Nelson, Heather | PhD | President's Professor |
| Bjorkland, George | PhD | Research Scientist |
| Bowman, Diana | | Co-PI |
| Brafman, David | PhD | PI |
| Buzinsky, Jade | BS | Graduate Student |
| Carbajal, Berta | | Research Specialist/Outreach and Recruitment |
| Carll, Phil | MSW | Research Specialist/Interventionist |
| Chen, Yanxi | MS | Graduate Researcher |
| Christiansen, Kendall | | High School Student |
| Conkle, Anderson | UG | Undergraduate Student |
| Conrad, Cheryl D. | PhD | |
| Coon, David W. | PhD | Director, Center for Innovation in Healthy and Resilient Aging; Professor |
| Corbin, Sierra | UG | Undergraduate Student |
| Cordova, Lourdes | | Research Specialist/Outreach and Recruitment |
| Demetri, Peter | | High School Student |
| Diaz, Zamira | UG | Undergraduate Student |
| Doyle, Rhys | UG | Undergraduate Student |
| Dzenga, Primrose | | Graduate Research Assistant |
| Essuman, Albert | MS | Graduate Researcher |
| Fani, Mahya | M.Arch | Doctoral Student, Graduate Service Assistance |

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|---|---|---|
| Frisch, Carlye | BS | Graduate Researcher |
| Glinka, Allison | MS | Project Coordinator |
| Guest, Aaron | PhD | Assistant Professor |
| Haas, Hannah | UG | Undergraduate Student |
| Highton, Lynn | UG | Undergraduate Student |
| Hook, Jane | MN, RN | Graduate Research Assistant |
| Johnson, Virginia | BS | Graduate Student |
| Kajitani, Keston | | Project Manager |
| Kelley-Wolfe, Kyria | UG | Undergraduate Student |
| Law, Olivia | BS | Graduate Assistant |
| Lewis, Candace | PhD | Assistant Professor |
| Leyasi, Salma | BS | Graduate Researcher |
| Lizik, Camryn | BS & BA | |
| Lukacik, David | | High School Student |
| Lyle, Tristan | BS, MS | Graduate Assistant |
| Melick, Alexandria | BS | Graduate Assistant |
| Mennenga, Sarah | PhD | Research Assistant Professor |
| Mitbander, Avantika | UG | Undergraduate Student |
| Mporanyi, Marlene | BS | Graduate Research Assistant |
| Nelson, Megan | UG | Undergraduate Student |
| Oevermann, Matthew | BS | Graduate Student Researcher |
| Olive, M. Foster | PhD | Associate Professor |
| Oyen, Emma | UG | Undergraduate Student |
| Palmer, Coree | UG | Undergraduate Student |
| Panagiotou, Eleni | PhD | PI, Assistant Professor |
| Pastor, Jade | UG | Undergraduate Student |
| Paulsen, Avery | UG | Undergraduate Student |
| Peckham, Allie | PhD | Assistant Professor |
| Pena, Veronica | PhD | Graduate Student Researcher |
| Plaisier, Seema | PhD | Staff Scientist |
| Pohl, Janet | PhD | Assistant Professor |
| Quintero, Carlos | | High School Student |
| Raghavan, Indu | PhD | Postdoctoral Researcher |
| Roorkeewal, Gandharva | UG | Undergraduate Student |

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|---|---|---|
| Ross, Heather | PhD | Principal Investigator |
| Sadow, Sage | BS | Research Technician |
| Salgado, Nazareth | | High School Student |
| Santos, Sydney | BS | Research Specialist/Interviewer |
| Schaefer, Sydney | PhD | Assistant Professor |
| Schulz, Philip | BS | Research Technician |
| Sharp, Nina | PhD | Assistant Professor |
| Sierks, Michael | PhD | Professor, PI |
| Squires, Alisa | | Graduate Research Assistant |
| Srinivasan, Gayathri | MS | Graduate Researcher |
| Stabenfeldt, Sarah | PhD | Associate Professor |
| Trevino, Jessica | MS | Project Coordinator |
| Truong, Vincent | | High School Student |
| Verpeut, Jessica | PhD | Principal Investigator |
| Vieira, Henrique | | High School Student |
| Wang, Yalin | PhD | Professor |
| Willingham, Crystal | MS | Laboratory Manager |
| Wilson, Melissa | PhD | Professor, Geneticist |
| Wu, Elizabeth | BS | Lab Manager |
| Yamada, Nelson | | High School Student |
| Yeom, Dongwoo Jason | PhD | Co-Investigator |
| Yun, Hyunsik | BS | Graduate Student |
| Zhu, Wenhui | MS | Graduate Researcher |

# BANNER ALZHEIMER'S INSTITUTE - PHOENIX

Banner Alzheimer's Institute's (BAI's) overarching goals are to find and support the approval and widespread availability of Alzheimer's disease (AD) prevention therapies as early as 2025; set a new standard of medical and non-medical care and support for cognitively impaired persons, at-risk persons, and their families; and forge models of multi-disciplinary, multi-institutional collaboration and resource sharing in biomedical research.

BAI has made pioneering contributions to the unusually early detection, tracking, study and diagnosis of AD, 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 AD, and the accelerated evaluation of disease-modifying and prevention therapies. It launched a new era in AD 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 as early as 2025, extend therapies to be administered at home as early as 2026 and identify primary prevention therapies in cognitively unimpaired persons at genetic risk who do not yet show biomarker evidence of amyloid plaques -- as early as 2027. 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 enrollment programs for Arizona's Native American and Hispanic/Latino communities, evaluates and follows Native Americans in the NIA-sponsored Arizona AD Research Center's (ADRC's) Clinical Core and oversees an annual conference on AD and Dementia in Native Americans. Its Banner Dementia Care Initiative seeks to optimize the identification and evaluation of cognitive problems, address a broad range of the affected person's and family's needs, reduce unnecessary hospitalizations and maintain affordability to health care payers.

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 with two, one and no copies of the APOE4 allele, 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-based biomarkers in the diagnosis and study of AD.

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 NIA-sponsored longitudinal brain imaging study of cognitively unimpaired persons with two copies, one copy and no copies of the APOE4 allele, reflecting three levels of genetic risk for late-onset AD, 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 AD kindred in Colombia. It was a founding member of the AD 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-sponsored research grants, 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-based biomarkers for AD and related disorders in their longitudinal cohorts to find and support the use of promising amyloid and other blood tests for AD 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 AD 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 effective AD 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 AD, including the very first AD prevention trial in Colombian members of the world's largest autosomal dominant AD (ADAD) kindred, who are virtually certain to develop AD and become cognitively impaired at the median age of 44. 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 as early as 2025, 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 web-based Alzheimer's Prevention Registry (www.endALZnow.org) has provided updates about advances in prevention research and opportunities to enroll in prevention 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 a growing number of AD prevention trials and related studies and developed suitable ways to inform interested 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 an amyloid-β blood tests), and address the logistical, ethical and scientific issues involved in this endeavor.

BAI's organizational aims include:

1. To leverage imaging resources in the early detection, tracking, and diagnosis of AD, 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 implement, evaluate and use PET radiotracer techniques (e.g., for the assessment of amyloid and tau pathology) in the study of AD and related disorders.

4. To develop image-analysis techniques and composite cognitive test scores with improved power to detect and track AD and evaluate AD-modifying and prevention therapies.

5. To accelerate the evaluation of AD prevention therapies through API's preclinical AD trials and enrollment registries.

6. To introduce a novel approach for the early phase evaluation of APOE and other AD-modifying drug and gene therapies using CSF and blood-based biomarkers in biomarker positive persons.

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 AD and related disorders, and to establish the generalizability of these methods to persons from under-represented Hispanic/Latino and Native American groups.

8. To support the evaluation of non-pharmaceutical prevention therapies intended to promote cognitive health.

9. To advance the science of research participant engagement and AD study participation, including in under-represented groups.

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 AD and related disorders as soon as possible, advance the roles of blood-based 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, and to develop and evaluate the cost-effectiveness of a dementia care program that better addresses the needs of patients and family caregivers in the Banner Health Accountable Care Organization in the Banner Dementia Care Initiative.

12. To support the clinical research and Native American outreach, education and enrollment goals of the Arizona ADRC.

13. To promote the further development, productivity, and close working relationships of research programs involved in the fight against AD and related disorders.

## BANNER ALZHEIMER'S INSTITUTE - PHOENIX

| Name (last, first) | Degree | Role on project |
|---|---|---|
| Alexander, Robert | MD | Chief Scientific Officer, Alzheimer's Prevention Initiative |
| Amador, Ricardo | | Clinical Research Program Manager |
| Ashton, Nicholas | PhD | Senior Director, Biomarker Program |
| Autry, Lynn | | Senior Psychometrist |
| Bandy, Daniel | | Associate Director, Senior Scientist |
| Battraw, Angelena | | Clinical Research Representative |
| Bauer lll, Robert | | Senior IT Systems Analyst |
| Boker, Constance | | Director, Imaging Center |
| Buco, Richmond Andre | | Senior Psychometrist |
| Chen, Yinghua | | Data Scientist |
| Copeland, Jacquie | PhD | Neuropsychologist |
| Devadas, Vivek | | Data Analyst |
| DiLise-Russo, Marjorie | | Senior Psychometrist |
| Ghisays, Kathryn | | Senior Clinical Research Program Manager |
| Ghisays, Valentina | PhD | Bioinformatics Scientist |
| Gonzalez-Green, Ricquee | | Clinical Research Coordinator |
| Gopalakrishna, Ganesh | MD | Associate Director, Memory Clinic |
| Goradia, Dhruman | PhD | Bioinformatics Scientist |
| High, Nellie | | Senior Clinical Research Program Manager |
| Jaeger, Chad | | Senior Director, COO Banner Research |
| James, Michelle | PsyD | Neuropsychologist |
| Joshi, Pallavi | MD | Physician - Dementia |
| Knox, Jennifer | | Clinical Research Coordinator |
| Koren, Andrei | PhD | Associate Director, Radiochemistry Lab |
| Langbaum, Jessica | PhD | Senior Director, Research Strategy<br>Co-Leader, Arizona ADRC Administration and Outreach, Recruitment and Engagement Cores |
| Langlois, Carolyn | | Associate Director, API Programs & Research |
| Lee, Wendy | | Senior Manager, Research Bioinformatics |
| Li, Shan | | Associate Bioinformatics Analyst |
| Liang, Winnie | PhD | Senior Scientist, Core Resources |
| Lomay, Nicole | | Senior Outreach Program Manager |
| Luo, Ji | | Data Scientist |
| Malek Ahmadi, Michael | PhD | Senior Bioinformatics Scientist |
| Martinez, Laura | | Clinical Research Coordinator |
| Mulder, Heather | | Associate Director, Outreach Research |
| Nisson, Lori | MSW/ LCSW | Director, Family & Community Services |
| Ochoa, Cassandra | | Senior Clinical Research Program Manager |
| Pandya, Sachin | | Senior Manager, Clinical Trials |

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|---|---|---|
| Parales, John | | Clinical Research Representative |
| Parkhurst, David | | Clinical Research Program Manager |
| Protas, Hillary | PhD | Bioinformatics Scientist |
| Pruzin, Jeremy | MD | Physician - Dementia |
| Rehban, Julia | | Clinical Research Lab Coordinator |
| Reiman, Eric | MD | CEO & CSO, Banner Research<br>Director, Arizona Alzheimer's Consortium (AAC)<br>Principal Investigator and Director, Arizona Alzheimer's Disease Research Center (ADRC) |
| Saner, Donald | MS | Senior Director, Research Data Science<br>Co-Leader, Arizona ADRC Data Management and Statistics Program |
| Schmitt, Andrea | | Arizona ADRC Administrative Director |
| Sohankar, Javad | | Bioinformatics Scientist |
| Starner, Mary Kate | | Clinical Research Coordinator |
| Su, Yi | PhD | Associate Director, Computational Brain Imaging Analysis Program; Co-Leader, Arizona ADRC Data Management and Statistics Core |
| Tariot, Pierre | MD | Director, Banner Alzheimer's Institute |
| Tsai, Po-Heng | MD | Associate Director, Clinical Trials |
| Vadovicky, Sheila | | Senior Psychometrist |
| Walsh, Trisha | | Associate Director, Observational Research Programs |
| Weidman, David | MD | Physician – Dementia; ADRC Clinical Site PI |

## 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. 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 to individuals, caretakers, and families in Tucson and Southern Arizona. The Lewy Body Dementia Center, led by its Medical Director, 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 dementia related diseases. In addition to these resources, individual and group cognitive training programs have recently been added to support patients with mild cognitive impairment (MCI) and plans are underway to incorporate programs on prevention of cognitive decline and 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), 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 assessment 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 examinations. 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 72 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 the Hispanic Outreach, Recruitment, and Retention project with Dr. Rapcsak serving as PI. Our efforts in the past year have increased the percentage of Hispanic/Latino ADRC participants from

23% to 30% and we have several additional Hispanic/Latino individuals who have agreed to join the study.

An important research mission for BAI-T is also 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 Dr. Rapcsak serving as Co-Investigator. These include studies on the use of non-invasive brain stimulation (TMS) to improve memory function and hippocampal plasticity in MCI (R21AG077153, RO1AG062543), using smart-phone based technology to track autobiographical thought as an early cognitive marker of AD (RO1AG068098), and developing new imaging methods to identify early changes in thalamic nuclei in neurodegenerative disease (RO1EB032674). We have two additional NIH grant applications currently under review focusing on the use of TMS to identify cortical hyperexcitability and cholinergic dysfunction in AD and a study on the contributions of mobility and spatial navigation skills to AD risk. We recently submitted another RO1 grant application focusing on the use of semantic memory assessment to identify early AD pathology, and also have an ongoing collaboration with UA researchers on the use of noninvasive brain stimulation to improve language function in logopenic primary progressive aphasia (PPA), which is funded by the AAC.

In addition to these studies, BAI-T investigators, including Dr's Allan Anderson, Matthew Malone, Bradley, and Rapcsak, along with our Clinical Trials team, currently conduct six active clinical trials. These trials include a Phase II EIP Pharma RewinD-LB Clinical Trial for patients with Dementia with Lewy Bodies (DLB), which is funded with support by a collaboration between EIP Pharma and the NIH. This trial began enrolling patients an August of 2023 and may bring us closer to the first approved therapy for patients living with DLB. Additional studies include a Phase III Cassava Sciences Refocus trial for patients with mild to moderate 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

| Name (last, first) | Degree | Role on project |
|---|---|---|
| Anderson, Allan | MD | Medical Director, Toole Family Memory Center, BAI Tucson |
| Anguiano, Jaynie | | Clinical Research Program Manager |
| Ashish, Dev | PhD | Clinical Neuropsychologist, Manager |
| Ayers, Amber | | Events Coordinator |
| Bradley, Kate | MD | Director, Movement Disorders, Toole Family Memory Center, BAI Tucson |
| Edmonds, Emily | PhD | Neuropsychologist |
| Guayante, Kristen | | Clinical Research Assistant |
| Jiminez, Jennifer Traslavania | | Psychometrist |
| Lindemer, Shannon | | Senior Psychometrist |
| Malone, Matthew | MD | Physician |
| Martin, Sarah | FNP-C | NP – Specialty Care |
| Pazzi, Marjorie | | Director, Clinical Trials |
| Parker, Cheryl | FNP-C | NP – Specialty Care |
| Rainey, Joseph Charles | | Clinical Research Representative |
| Rapcsak, Steven | MD | Associate Director, Clinical Trials |
| Rico, Kristina | | Clinical Research Coordinator |
| Robinson, Jaclyn | MD | Physician - Dementia |
| Schubert, Corey | | Marketing/Public Relations Director |
| Teposte, Mariana | | Clinical Research Assistant |

# BANNER SUN HEALTH RESEARCH INSTITUTE

Banner Sun Health Research Institute (BSHRI) is a world-renowned Alzheimer's disease (AD) and Related Disorders (ADRD), and cognitive aging, research and clinical care institute 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 includes: a) An internationally renowned Brain and Body Donation Program (BBDP) for the study of AD/ADRD, PD, related disorders, cancer and aging; b) 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 Centers, The Division of Neuropsychology, and Family and Community Services; c) More than 35 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; d) The Center for Healthy Aging, with a Longevity Longitudinal Cohort Study of cognitive aging in older individuals with over 1,614 research participants (479 active) (~70% female, 307 are ≥80 years of age, 157 are ≥85, 73 are between 90-99, and 6 >100 years); and a free, community service, Brain Health Check-In (BHCI) Program (>850 performed since December 2018) to provide walk-in or scheduled brain health concern assessments along with feedback, information, education, resources and referrals; e) Extensive outreach, education, training and volunteer programs including >130 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; f) Leadership roles and close working 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; and g) Where historically, the state's largest number of productive basic scientists in the fight against AD, who were known for their major contributions to the study of amyloid and tau processing, brain inflammation, epigenetics, and the roles of cholesterol and cerebrovascular disease in AD, were located prior to 2017 (these basic science programs have since relocated to ASU). From 2001-2016, BSHRI served as the applicant organization for the Arizona ADCC on behalf of the organizations in the Arizona Alzheimer's Consortium (ACC), and it remains home to the ADCC's Administrative Director, Andrea Schmitt, and multiple AARC consortium leaders including Drs. Alireza Atri, Geidy Serrano, and Thomas Beach.

The internationally renowned BBDP, directed by Thomas Beach, MD, PhD and Dr. Geidy Serrano, include ~600 actively followed (~5,000 total enrolled since inception), clinically characterized and longitudinally assessed participants, 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. All participants consent to donate their brains and/or bodies after death. 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 >3,000 expired donors, who have had comprehensive assessments during life and neuropathological examinations after death; b) an unusually 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 >780 expired donors since 2005, and the opportunity to relate brain pathology to biological features of other body organs; and d) distributed a total of 20,000 biospecimens through 255 shipments distributions to advance research in Arizona and around the world (>1,000 shipments in the last 5 years; in 2023 shared 117 samples with Arizona scientists, 116 shipments to scientists in 19 other US states, with 20 shipments to international scientists). The BBDP includes many research participants in the AZ ADCC's Clinical and Ancillary BBDP Cores and the ADCC's Neuropathology Core, in partnership with Mayo Clinic AZ and Barrow Neurological Institute. In addition, it continues to play critical roles in the neuropathological validation of amyloid-, tau- and synaptic(SV2A)-PET and other ante-mortem biomarkers, thus contributing to assessment and FDA approval of molecular imaging/PET, CSF and blood-based biomarkers for AD/ADRD. The BBPD provides a critical tissue resource for genome-wide genetic, transcriptomic and proteomic data from different brain regions and cell types, and contributes to numerous research studies, collaborations, grants, and dozens of annual publications and impactful findings.

BSHRI has undergone significant changes since 2016, shifting focus from basic sciences to clinical and translational science and clinical services, and setting the stage for BSHRI and its organizational partners to further develop its AD/ADRD, PD and movement disorders, and aging clinical, research, education, training and outreach programs. These changes include: a) Ongoing harmonization of Banner Alzheimer's Institute's AD/ADRD-related clinical, family and community services, clinical research and clinical trials programs on its downtown Phoenix and BSHRI campuses including launching and housing the Dementia Care Partners community care navigation and support program; b) Further growth of comprehensive and integrated multidisciplinary services at The Cleo Roberts Memory and Movement Disorders Centers including recruitment of several clinicians/clinician-scientists; c) Successful implementation of innovative services, clinical and research (e.g. brain health check-in, ultrasound LP via a past AAC grant) d) Successful launch and expansion of the Brain Health Check-In (BHCI) community service program at the Center for Health Aging; (since December 2018 these walk-in or scheduled BHCIs have provided >850 individuals with free brain health concern status assessments along with feedback, information, education, resources and referrals); e) Substantially enhancing clinical and biological (biofluid/serum) characterization of the BSHRI's Longevity Study cohort (see current AAC report of funding, Dr. Alireza Atri PI), and harmonizing important elements and increasing co-enrollment in the Longevity Study and BBDP programs; f) Ongoing strategic planning for the development and further growth of clinical, aging and clinical/translations research programs, services, and training and education programs on the BSHRI campus -- in addition to BSHRI's large clinical, family and community services, and clinical trials programs, its scientific, education and outreach efforts include >130 international, national, regional, and community presentations per year; BSHRI staff provided >15,000 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); g) Expanding the BBDP in impactful ways, including >3,000 research visits in ~600 annually assessed prospective brain donors; inclusion of blood, CSF and/or imaging data and samples in many BBDP participants; and development of a public resource of sorted cells, and a resource of omics data from different cell types and regions that differ in the vulnerability and resilience to elements of AD pathology (to help us and our TGen, NDRC and other 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 (in 2022) AZ Alzheimer's Disease Research Center (ADRC; P30 expanded NIH funding mechanism that replaced the AZ Alzheimer's Disease Center, ADC).

## BANNER SUN HEALTH RESEARCH INSTITUTE

| Name (last, first) | Degree | Role on project |
|---|---|---|
| Atri, Alireza | MD, PhD | Director, Banner Sun Health Research Institute |
| Beach, Thomas | MD, PhD | Director, Brain and Body Donation Program |
| Al Jubouriy, Hamzah | | Clinical Research Assistant |
| Arce, Richard | | Organ Donor Technician |
| Arch, Autumn | PhD | Post Doctoral Fellow, Neuropsychology |
| Ashton, Nicholas | PhD | Senior Director, Biomarker Program |
| Aslam, Sidra | | Bioinformatics Analyst |
| Auman, Briana | PsyD | Neuropsychologist |
| Beh, Suet Theng | PhD | Staff Scientist |
| Belden, Christine | PsyD | Director, Neuropsychology |
| Blake, Lauren | PsyD | Neuropsychologist |
| Borja, Claryssa | | Senior Pathology Technician |
| Brown, Victoria | | Clinical Research Assistant |
| Castaneda, Manelly | | Research Assistant |
| Choudhury, Parichita | MD | Physician - Dementia |
| Cline, Carol | | Psychometry Coordinator |
| Cline, Madison Paige | | Senior Pathology Technician |
| Davis, Kathryn | | Senior Psychometrist |
| Delgado, Jaztine | | Clinical Research Assistant |
| Evans, Brittani | | Neuropsychology Assistant |
| Glass, Michael | | Psychometrist |
| Gregory, Daysia | | Clinical Research Assistant |
| Gulmen, Mine | | Research Assistant |
| Hemmingsen, Spencer | | Pathology Technician |
| Ho, Andrew | PhD | Medical Resident |
| Intorcia, Anthony | | Manager, Pathology |
| Johnson, Natalie | | Clinical Research Assistant |
| Jooste, Carla | | Clinical Research Assistant |
| Krupp, Addison | | Pathology Technician |
| Kuramoto, Angela | | Senior Manager, Clinical Trial |
| Liebsack, Carolyn | | Director, Clinical Trials |
| Long, Kathy | | Clinical Research Representative |
| Lorenzini, Ileana | | Neuropathology Research Scientist |
| Mariner, Monica | | Tissue Donation Coordinator |
| McHattie, Rylee | | Pathology Technician |

| | | |
|---|---|---|
| Moorefield, Paula | | Business Support Assistant |
| Moorley, Naudia | PsyD | Psychometry Coordinator |
| Napierkowski, Madelynn | | Clinical Research Assistant |
| O'Connor, Kathleen | | Clinical Research Coordinator |
| Orozco, Richard | | Clinical Research Assistant |
| Post, Brett | | Clinical Research Assistant |
| Qiji, Sanaria | | Pathology Technician |
| Rangel, Amy | | Phlebotomist Coordinator |
| Reyes, Priscilla | | Psychometrist |
| Rosalez, Sirena | | Psychometrist |
| Sakhai, Sherwin | | Post Doctoral Fellow, Neuropsychology |
| Serrano, Geidy | PhD | Director, Neuropathology Lab |
| Shaikh, Farah | | Clinical Research Assistant |
| Shprecher, David | DO | Movement Disorders Program Director, Neurologist |
| Shull, Anissa | | Pathology Technician |
| Soza, Vanessa | | Clinical Research Assistant |
| Stewart, Analisa | | Pathology Technician |
| Surdyn, Michelle | | Tissue Donation Support Navigator |
| Suszczewicz, Katsuko | | Pathology Technician |
| Teran, Marlene | | Clinical Research Assistant |
| Wermager, Zekiel | | Pathology Technician |
| Walker, Jessica | | Research Project Coordinator |
| York, Kylee | | Senior Psychometrist |

## 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 provide care partners with information, practical tips, and support to overcome challenging aspects of providing care. A "Creating My Way, Day-By-Day" workshop series that provides crucial decision-making information to the care partners of patients with early to moderate dementia. 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 Parunyou Julayanont, 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 2022 and 2023, program clinicians led 23 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 and various studies of new approaches to disease-modifying treatments, including monoclonal antibodies against pathological protein targets such as amyloid and p-tau, neuromodulation therapies, and therapies that improve cognitive function by stabilizing tau proteins. They continue to be a leader in pushing the boundaries of care through novel neurosurgical approaches, such as deep brain stimulation for Alzheimer's. 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 that are currently underway and in development. Support from the Arizona Alzheimer's Consortium (AAC) has boosted the development of 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 Hispanic/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 (RF1AG061566) to investigate the genetic signature of tau neurons during the progression of AD.

Associate Professor Sylvia Perez, PhD, focuses on studying the molecular mechanism underlying the neuropathology associated with cognitive decline and dementia in Alzheimer's disease (AD), Down syndrome and traumatic brain Injury. Dr. Perez was recently awarded funding from the NIH to examine cognitive decline at the cellular and molecular level in Down syndrome (RF1AG081286), laying the foundation for a wide range of potential drug interventions that may translate to the treatment of AD.

Assistant Professor David Medina, PhD, specializes in investigating neurodegenerative diseases including ALS, FTD, and AD, with a particular focus on identifying new molecular pathways using cellular and mouse models. His work employs multidisciplinary approaches utilizing and developing drug delivery techniques, multiomics, behavioral analysis, and in vitro modeling. 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 common mechanisms of disease in AD and ALS. His research endeavors also involve the evaluation of innovative therapeutic strategies, which include small molecules, novel nanoparticle formulations, and viral

vector approaches. Dr. Medina serves as PI in a multiyear Therapeutic Idea Grant from the US Department of Defense (AL2020-61), which supports the development of gene therapy approaches targeting the retinoid signaling pathway for ALS and other neurodegenerative conditions.

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 and the Skylight Charitable Trust. This past year (2023-24), 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, R21NS125861), the role of RNA processing in TDP-43 pathology (R01NS091299, 1R21NS130492) and mechanisms of neurodegeneration in LBD (R21NS128550), in addition to $700K from the Department of Defense on the mechanisms of synaptic protein dysfunction and therapeutic opportunities for synapse regeneration (AL200139; AL230149). Finally, together with Multi-PIs Drs. Sabbagh 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 Alzheimer's disease and related dementias (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

| Name (last, first) | Degree | Role on project |
|---|---|---|
| Acothley, Skieff | BS | Research Assistant |
| Baez Cruz, Jessica | BS | Psychometrist |
| Bakkar, Nadine | PhD | Neuroscientist; Assistant Professor, Translational Neuroscience |
| 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 |
| Cunningham, Shawna | MS | Senior Research Tech |
| Garcia, Angelica | BS | Study Coordinator |
| Garcia Suarez, Jonathan | BS | Research Assistant |
| Geda, Yonas | MD | Behavioral Neurologist |
| Gopalakrishnan, Lathika | PhD | Post-doctoral Research Fellow |
| Hanson, Krista | PhD | Neuropsychologist |
| He, Bin | MD | Research Associate |
| McLean, Amy | DNP | Nurse Practitioner |
| Medina, David | PhD | Neuroscientist; Assistant Professor, Translational Neuroscience |
| Moreno, Marta | PhD | Post-doctoral Research Fellow |
| Mufson, Elliott | PhD | Neuroscientist; Professor of Neurobiology |
| Perez, Sylvia | PhD | Neuroscientist; Associate Professor, Translational Neuroscience |
| Preller, Kim | BSc | Research Technician |
| Quezada, Giselle | BS | Research Technician |
| Sabbagh, Marwan | MD | Geriatric Neurologist; Vice Chair of Research |
| Santiago, Jalisa | BS | Clinical Research Assistant |
| Sattler, Rita | PhD | Neuroscientist; Professor, Translational Neuroscience |
| Shill, Holly | MD | Neurologist; Director, Movement Disorders Program |
| Snell, Margeaux | MD | Program Manager |
| Stokes, Ashley | PhD | Neuroscientist; Assistant Professor, Neuroimaging Innovation Center |

## 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 73 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 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

| Name (last, first) | Degree | Role on project |
|---|---|---|
| Jacobsen, Colleen | | Project Manager, Critical Path for Alzheimer's Disease |
| Karten, Yashmin | PhD, MPH | Scientific Director, Critical Path for Alzheimer's Disease |
| Lau, Corissa | MBA | Project Manager, Critical Path for Alzheimer's Disease |
| Leuzy, Antoine | PhD | Principal Investigator; Neuroimaging & biomarkers |
| Priest, Eileen | | Project Coordinator, Critical Path for Alzheimer's Disease |
| Romero, Klaus | MD, MS | Chief Executive Officer, Chief Science Officer |
| Stephenson, Diane | PhD | Interim Executive Director, Critical Path for Alzheimer's Disease |

## 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 potential plasma biomarkers (APOE fragments and others). 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's Institute, Barrow Neurological Institute, Arizona State University, 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. Len Petrucelli and Matthew Baker at Mayo Clinic Florida. Our bench neuroscience is being carried out by Dr. John Fryer who works primarily with animal models. Through additional philanthropic support we have performed MRIs on more than 160 members and whole genome sequencing on the 527 members of this cohort for whom we had stored DNA further fostering collaboration and extending our range of scientific inquiry. We also are in the process of analyzing a large cohort of resilient agers through a collaboration with Drs. Owen Ross and Neill Graff-Radford from Mayo Clinic Florida, as well as the impact of recent novel genetic risk factors on cognitive aging trajectories. Two Mayo Clinic Arizona investigators were awarded competitive funding by the Arizona Alzheimer's Consortium. Dr. Oana Dumitrascu is studying retinal changes of Alzheimer's disease (AD) in clinical and preclinical cohorts, while Dr. Zonghui Ding is studying bispecific antibodies targeting both amyloid-β and α-synuclein to expand treatment options for these two common neurodegenerative proteinopathies. Drs. Leslie Baxter and Bryan Woodruff will serve as co-investigators for a multisite collaborative study with Dr. Blair Braden at Arizona State University evaluating aging outcomes in autistic adults. We also welcome the addition of two additional clinician-scientists to our team. 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 recently joined the Division of Nuclear Medicine at Mayo Clinic Arizona, bringing her expertise in advanced metabolic and molecular imaging techniques applied to neurodegeneration.

Our longitudinal study design is a unique strength with our longest participants having been followed for 29 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 the neuropsychologically defined onset of Alzheimer's disease begins in APOE e4 carriers in their 50s, is confined to memory during the early preclinical phase but there is 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 a 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.

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. Inform the design of primary and secondary prevention clinical trials.
5. Provide 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. Determine the relative time course 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. Contribute 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.

This research proposal has been peer reviewed and approved by the Mayo Clinic Institutional Review Board (IRB #259-99).

## MAYO CLINIC ARIZONA

| Name (last, first) | Degree | Role on project |
|---|---|---|
| Woodruff, Bryan | MD | Principal Investigator, Behavioral Neurologist |
| Caselli, Richard | MD | Co-Investigator, Behavioral Neurologist |
| Locke, Dona | PhD | Co-Investigator, Neuropsychologist |
| Wicklund, Meredith | MD | Co-Investigator, Behavioral Neurologist |
| Dumitrascu, Oana | MD | Co-Investigator, Cerebrovascular Neurologist, Neuro-ophthalmologist |
| Adler, Charles | MD, PhD | Co-Investigator, Movement Disorder Neurologist |
| Chiu, Shannon | MD, MS | Co-Investigator, Movement Disorder Neurologist |
| Baxter, Leslie | PhD | Co-Investigator, Neuroimaging Scientist, Neuropsychologist |
| Koran, Mary Ellen | MD, PhD | Co-Investigator, Nuclear Medicine Radiologist |
| Fryer, John | PhD | Co-Investigator, Neuroscientist |
| Ding, Zonghui | MD, PhD | Co-Investigator, Neuroscientist |
| Stonnington, Cynthia | MD | Co-Investigator, Psychiatrist |
| Dumkrieger, Gina | PhD, MS | Principal Data Science Analyst |
| Nikolova, Simona | PhD | Data Analyst |
| Langlais, Blake | MS | Principal Biostatistician |
| Ezenne-Nwoye, Adaeze | MSN, RN, APRN, FNP-C, BSN | Nurse Practitioner |
| Brostrom, Debra | BA | Study Coordinator |
| McCarty, Monica | CRC | Study Coordinator |
| Polgar, Emily | CRC | Study Coordinator |
| Klopotowski, Natalia | CRC | Study Coordinator |

## 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. Most recently, Midwestern created a Metabolism Center of Excellence to support research into metabolism and metabolic disorders. Our Veterinary Medicine program has brought with it many new research opportunities 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. 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, patient evaluation and treatment mechanisms, education and outreach, and clinical recruitment.

Current Alzheimer's research-related aims at Midwestern include:

1. Understanding the potential role of microbes in the development of AD brain pathology and cognitive deficits. This research involves studies of 1) human post-mortem tissues, including patients with both AD and MCI in comparison to normal and high pathology non-demented

controls, 2) infection of 3xTG and APOE4 mice to test if infection with common microbes can exacerbate pathology in these models and 3) evaluation of gut microbiome changes in 3xTg and APOE3/4 mice.

2. Studying the effect of various diets, exercise regimens and therapeutic compounds on the development of risk factors for Alzheimer's disease including cardiovascular disease, type 2 diabetes, insulin resistance, and inflammation. 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.
3. Evaluating the role of progranulin in Alzheimer's disease. Progranulin is a protein which shows functional alterations in transport and lysosomal processing early in the development of Alzheimer's pathology. 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.
4. Applying geroscience to the study of 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 using the same mouse model.
5. Exploring the role of the RAP1 protein in the molecular steps leading to the development of Alzheimer's disease. RAP1 is a protein that protects the chromosome ends (telomeres) against shortening over time. Shortening of the telomeres is associated with cellular aging and increases with advancing age, which is the greatest risk factor for AD. RAP1 may also have additional functions relevant to 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 and 2) further exploration of the ability of RAP1 to bind not only to telomeres but also to other binding sites within the genome.
6. Examining a proposed link between a protein that protects the chromosome ends against shortening (RAP1) and a protein localized to astrocytes (GFAPδ), which also interacts with presenilin-1. Telomere shortening is a molecular cause of cellular aging, and advancing age is the greatest known risk factor for AD. This project studies the possibility that GFAPδ variants will modulate the accumulation of amyloid deposits in a cell culture model. This study also evaluates the ability of RAP1 and GFAPδ to activate gamma-secretase as well as the DNA-binding properties of RAP1.
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.

## MIDWESTERN UNIVERSITY

| 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 |
| Bae, Nancy | PhD | Principal Investigator |
| Broderick, Thomas | PhD | Principal Investigator |
| Bussey, Kimberly | PhD | MAAC Investigator |
| Call, Gerald | PhD | Principal Investigator |
| Castro, Monica | BS | Research Coordinator |
| Christensen, Stephanie | PhD | Co-Investigator |
| Chu, Ping | BS | Sr. Research Specialist |
| Day, Samantha | PhD | MAAC Investigator |
| 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 |
| Gerber, Dawn | PharmD | MAAC Investigator |
| Gonzalez, Fernando | PhD | MAAC Investigator |
| Haley, Nick | PhD | MAAC Investigator |
| Halket, Christine | DDS | MAAC Investigator |
| Hernandez, Jose | PhD | MAAC Investigator |
| Huang, Vanthida | PharmD | MAAC Investigator |
| Hughes, Tiffany | PhD, MPH | MAAC Investigator |
| Hull, Elizabeth | PhD | Principle Investigator |
| Jones, Carleton | PhD | MAAC Investigator |
| Jones, Douglas | PhD | MAAC Investigator |
| Jones, T. Bucky | PhD | Principal Investigator |
| Kaufman, Jason | PhD | MAAC Investigator |
| Korch, Shaleen | PhD | Principle Investigator |
| Kozlowski, Michael | OD, PhD | MAAC Investigator |

| | | |
|---|---|---|
| Lawson, Kathy | PhD | MAAC Investigator |
| Lewis, Kelsey | BS | Research Specialist |
| Leyva, Kathryn | PhD | Principle Investigator |
| Li, Weidang | PhD | MAAC Investigator |
| Olsen, Mark | PhD | MAAC Investigator |
| Potter, Pamela | PhD | MAAC Investigator |
| Potter, Ross | PhD | Research Coordinator |
| Revill, Ann | PhD | Principal 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 | Principal Investigator |
| Vallejo-Elias, Johana | PhD | MAAC Investigator |
| Veltri, Charles | PhD | MAAC Investigator |
| Weissig, Volkmar | PhD | MAAC Investigator |
| Whetzel, Alexis | BS | Research Specialist |
| Yevseyenkov, Vladimir | OD, PhD | MAAC 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 transplants 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 family caregivers ("care dyads") living in rural areas. 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 caregivers because these individuals are at an elevated risk of transitioning to Dementia due to AD. Research on early detection and support among individuals with MCI due to AD and their 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 care dyads with MCI. We are partnering with senior centers throughout the Northern Arizona region to determine care dyad 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 care dyads' 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. In our first year of funding, our team reached out to 23 senior centers in Coconino, Apache, Gila, Mojave, Navajo, and Yavapai counties. So far, six center leaders responded representing approximately 380 center patrons from diverse races and ethnicities and speaking languages including English, Spanish, Diné bizaad, Mojave, Havasupai, and Hopi. Data collection is ongoing, with 18 participants (9 individuals with MCI, 9 caregivers) completed or currently enrolled in the study.

## NORTHERN ARIZONA UNIVERSITY

| Name (last, first) | Degree | Role on project |
|---|---|---|
| McCarthy, Michael | PhD | Co-PI |
| McCoy, Megan | PhD | Co-PI |
| Cerino, Eric | PhD | Co-PI |
| Cope, Emily | PhD | PI and Project Director |
| Caporaso, J Gregory | PhD | PI |
| Traustadottir, Tinna | PhD | PI |
| Schwartz, Egbert | PhD | Co-I |
| Lifshitz, Jonathan | PhD | Collaborator |
| Barnes, Carol | PhD | Collaborator |
| Keim, Paul | PhD | Executive Director, PMI |
| Martinez, Margarita | MSW | Graduate Masters Student (Graduated) |
| Anderson, Travis | BSW | Graduate Masters Student |
| Horowitz, Chloe | MA | Graduate Masters Student (Graduated) |
| Taylor, Zachary | MA | Graduate Masters Student (Graduated) |
| Wicker, Alexander | BS | Undergraduate Researcher (Graduated) |
| Seaton, Thomasina | BS | Graduate Masters Student |
| Goldtooth, Amanda | BS | Graduate Masters Student |
| Livingston, Raechel | BS | Graduate Masters Student |
| Dopson, Rasheera | MPH | Graduate PhD Student, NARBHA Scholar |
| Lucero, Louis | BS | Community Partner, Director of the Joe C Montoya Community and Senior Center (Flagstaff, AZ) |
| Herman, Chloe | BS | Graduate Student |
| Borsom, Emily | PhD | Graduate Student (former) |
| Conn, Kathryn | BS | Graduate Student |
| Hagen, Johanna | BS | Research Software Engineer |
| Rodriguez, Dominick | BS | Graduate Student |
| Barroso, Daisy | BS | Graduate Student |
| Dikshit, Shreya | | Undergraduate Researcher |
| McNeal, Jaliyah | | Undergraduate Researcher |

# TRANSLATIONAL GENOMICS RESEARCH INSTITUTE

The Translational Genomics Research Institute (TGen) is a non-profit biomedical research institute whose mission is to make and translate genomic discoveries into advances in human health. TGen is dedicated to bringing the breakthroughs in genomics research to the bedside and benefit of patients. Its focus on translational research involves coupling, in novel ways, basic and clinical science with emerging molecular technologies to accelerate the development of therapeutics and diagnostics for human disease. Part of the unique nature of TGen is its collaborative relationships with academic institutions, clinical practices and corporate entities, each aimed at accelerating discovery-based research towards application.

The Neurogenomics Division of TGen is the home of Alzheimer's disease (AD) and aging research programs within TGen. AD and aging have been a focus of the Division since its inception. The Neurogenomics Division is subdivided into several disease-oriented research clusters. Each cluster represents a unique cross-pollination between basic researchers and clinicians with the endgame being successful clinical trials that ultimately lead to improved treatments and diagnosis. These clusters include geneticists, molecular and cellular biologists, brain imaging researchers, proteomics specialists, drug development teams, and other experts.

The Division has accomplished several milestones in AD research including: (1) the first high-density genome screen to identify common heritable risk factors for AD, (2) the identification of a key genetic driver of episodic memory function in healthy individuals, (3) the first large-scale study identifying cell-specific genes differentially expressed in pathology-containing and pathology-free neurons in the brains of AD patients and control donors, (4) the identification of protein kinase targets responsible for phosphorylation of the tau protein which contributes to AD pathology and the use of this information to identify novel therapeutic approaches to the disease, (5) the collaborative discovery of a novel cognitive enhancing agent based on the genetic finding in episodic memory, and (6) the identification of new, cell-free extracellular vesicle biomarkers in the blood of AD patients. Collaborations within Arizona and across the nation have been critical for each of these projects and they included work with Arizona State University, Banner Alzheimer's Institute, University of Arizona, Banner Sun Health Research Institute, Barrow Neurological Institute, the National Institutes of Health, and many others.

Currently the Division has major areas of focus in the genetic basis of disease in rare AD clinical cases (using next generation DNA sequencing), the characterization of the transcriptome of multiple cell types in the AD brain (using laser capture microdissection and single cell sequencing approaches), cell-free fluid biomarker identification (using extracellular vesicle molecular profiling), and novel drug development for cognitive enhancement and AD. The Division also serves as an AD-related genomics and biostatistics resource for the Arizona Alzheimer's Consortium and frequently assists in generation and interpretation of genotyping and sequencing data.

Overall, the mission of the Division's work in AD is to develop improved ways to assess personalized risk for AD before the onset of symptoms, leverage molecular information to identify novel drug targets, and gain deeper understanding of the genomic changes associated with disease onset and progression.

## TRANSLATIONAL GENOMICS RESEARCH INSTITUTE

| Name (last, first) | Degree | Role on project |
|---|---|---|
| Adamson, Sydney | BS | Research Associate |
| Alsop, Eric | MS | Computational Scientist |
| Antone, Jerry | BS | Research Associate III |
| Beres, Steven | BS | Research Associate I |
| Bonifitto, Anna | MS | Lab Manager |
| DeBoth, Matthew | BS | Bioinformatician |
| Ecco, Fabrizio | PhD | Postdoctoral Fellow |
| Glosh-Halder, Tithi | PhD | Postdoctoral Fellow |
| Huentelman, Matthew | PhD | Principal Investigator |
| Johnson, Megan | BS | Bioinformatician |
| Lechuga, Cynthia | MBA | Manager, Grants & Contract & System Support Administrator |
| Metz, Danielle | BS | Clinical Research Coordinator |
| Moore, Bethine | BA | |
| Mosqueda, Mario | BS | |
| Naymik, Marcus | MS | Bioinformatician II |
| Ng, Serina | BS | Research Associate |
| Nicholson, Leigh | PhD | Research Assistant Professor |
| Palade, Joanna | PhD | Staff Scientist |
| Palomares, Dorothy | BS | Research Associate |
| Piras, Ignazio | PhD | Research Associate Professor |
| Reiman, Rebecca | BA | Lab Manager |
| Robles, Laura | MBA | Project Accountant |
| Sharma, Sunil | MD, PhD, FACP, MBA | Co-Investigator |
| Soldi, Raffaella | PhD | Co-Investigator |
| Stark, Bobbi | BS | Research Associate II |
| Taguinod, Francis | MS | Research Associate II |
| Van Keuren-Jensen, Kendall | PhD | Co-Investigator |

# 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. Investigators engaged in these research projects represent fifteen departments and institutes in four colleges, encompassing the fields of neuroimaging, biomedical engineering, physics, neuroscience, cognitive neuroscience, neuropsychology, speech pathology, neurology, cardiology, surgery, pharmacology, physiology, 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 Arizona Alzheimer's Consortium (AAC) at UA provides pilot grants to researchers engaged in innovative projects that include a range of scientific approaches from basic neuroscience to clinical interventions and translate across human and non-human animal models of aging and disorders of aging. A major strength at UA is the development and utilization of novel magnetic resonance imaging (MRI) methods 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. These advances in MRI methods, image analysis pipelines, and neuroscience methods not only benefit researchers at UA but are also shared widely across the entire research community.

The AAC pilot project program at UA continues to be extraordinarily successful. In 2023/24, researchers funded by the AAC were awarded $9,014,315 in extramural grants from NIH, NIA, NIGMS, DOD, NSF, NHLBI, NINR, NIBIB, NIDA, SBIR, NBIB, USDA, and NIFA, among others. More than $35,000,000 in pending grants have also been submitted. A full list of these grants are provided later in this report.

Last year, UA was awarded a $2,000,000 high-end instrumentation (HEI) grant from NIH to support the acquisition of a next-generation Siemens Cima.X MRI scanner, which is scheduled to be installed in fall 2024. UA is one of the first sites in the country to obtain this state-of-the-art magnet that promises to significantly enhance our imaging capabilities. To further extend the utility of this new platform, funds from the AAC were used this year to outfit the new magnet with peripherals and electronics to expand capabilities for innovative research.

UA's researchers engage in translational research that spans multiple areas of expertise and methods to address clinical and basic research questions concerning the effects of healthy and pathological aging. These include investigating and tracking the neural systems and associated cognitive processes that are altered during the course of 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.

Details of each pilot project and their progress over the past year are included below. Here, we provide an overview of program-related activities at the UA in several major areas of research:

***Novel methods for MRI acquisition and image analysis.*** We continue to develop novel MRI pulse sequences and analysis methods which, together with extensive raw imaging data, are made available to the research community through XNAT, an NIH-funded online repository for neuroimaging data. The complexity and high cost of collecting and analyzing large-scale datasets highlights the importance of sharing raw data and methods throughout the research community. These methods have proven useful for examining brain structure, function, connectivity, and pathology in both human and non-human animal models of aging and age-related disease.

Over the past year, AAC pilot funding was provided to a) develop a novel method for network analysis of MRI data (Alexander), b) increase resolution of T2 and T1 MRI mapping for more accurate measurement of hippocampal subfields (Altbach), c) utilize quantitative perfusion MRI for evaluating perfusion and blood-brain barrier (BBB) integrity in older adults (Ryan), d) implement multispectral two-photon microscopy for measurement of BBB integrity in an AD mouse model (Trouard), and e) purchase MRI peripherals and electronics to expand research capabilities on the new Siemens 3T Cima.X MRI which is scheduled for installation in fall, 2024.

***Risk factors for age-related cognitive impairment and 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 identifying and understanding the factors that increase risk for age-related cognitive impairment and AD and their underlying neural mechanisms. These include studies of a) the impact of life-long physical exercise and sleep quality on age-related cognitive function (Alexander), b) the connection between the microbiome and cognitive functioning among healthy older adults (Barnes) c) the relationship between mircrobiome and Ab and tau pathology in older adults with MCI (Chou), d) the positive impact of imaginative thinking on cognitive function and the neural correlates of imaginative thinking measured by MRI (Grilli), e) the differential impact of stress and cortisol levels on cognitive function among Hispanic and non-Hispanic older adults (Ryan), and f) the impact of carotid disease on cognitive functioning among older adults (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 non-human animal models. They have the potential to identify targets for intervention as well as identifying sensitive biomarkers that can be used to track brain changes associated with aging and age-related disease. This year, studies included a) implementation of high-density probes for recording neuronal network activity in freely-moving mouse models (Cowen), and b) an investigation of the hippocampal--prefrontal circuitry mediating memory function, measuring ensemble-level neural activity in freely moving rats (Cowen). In several mouse models of AD, a series of studies determined the impact on cognitive dysfunction of c) vascular dysfunction (de Silva), d) inflammation (Rodgers), e) lipid dysfunction and lipid toxicity, and f) reactive astrogliosis in response to inflammation (Yin). Another study f) validated a novel method for detecting low-concentration Amyloid beta (Ab) in human AD brain tissue (Su).

***Potential interventions for cognitive impairment.*** Several studies evaluated novel interventions that may decrease risk for age-related cognitive impairment and/or AD, slow the progression of AD, or ameliorate cognitive impairments associated with normal aging and AD. These included a) a promising anti-inflammatory therapy targeting the renin-angiotensin system in the brain (angiotensin 1-7) in heart failure patients at high risk for developing vascular dementia, b) novel language therapy for individuals with AD with progressive aphasia (Kielar), c) interventions for carotid disease (Zhou), and d) transcranial magnetic stimulation to improve memory among individuals with MCI (Chou).

## UNIVERSITY OF ARIZONA

| Name (last, first) | Degree | Role on project |
|---|---|---|
| Ahanonu, Eze | MSc | Graduate Assistant |
| Alexander, Gene | PhD | Principle Investigator, Director, Brain Imaging, Behavior, & Aging Laboratory |
| Ally, Madeline | BA | Graduate Research Assistant |
| Altbach, Maria | PhD | Principal Investigator |
| Andrews-Hanna, Jessica | PhD | PI |
| Barnes, Carol | PhD | Director, Arizona Alzheimer's Consortium (AAC) and NIA-supported Arizona ADCC, Project director, data analysis, writing |
| Beach, Thomas | MD, PhD | Director, Brain and Body Donation Program |
| Bedoya, Arianna | MPH | Coordinator |
| Bharadwaj, Pradyumna | MA | Graduate Research Assistant |
| Bilgin, Ali | PhD | Co-I |
| Cameron, Raelyn | BA | Research Technician |
| Campos, Elena | BA | Undergraduate Research Assistant |
| Carrillo, Karina | BS | Coordinator |
| Chang, Hangbin | MS | PhD Student |
| Chawla, Monica | PhD | Associate Research Scientist |
| Chen, Yu-Chin | MD, PhD | Postdoc Researcher |
| Chou, Ying-hui | ScD | Associate Professor of Psychology at University of Arizona |
| Cowen, Stephen L. | PhD | Project director, data analysis, writing |
| Fatema, Arisha | BS | Undergraduate Research Assistant, BME, UA |
| Fernandez, Fernando | BS | Research Technician, Health Sciences and Brain Science |
| Frazier, Noah | | Undergraduate Research Assistant, Undergraduate Research Project |
| Gaffney, Kevin | PhD | Investigator, Pharmacology |
| Gin, Adley | PhD | PhD student |
| Gopalan, Radha | MD | Physician |
| Guarena, Lesley | MS | Graduate Student, Psychology |
| Green, Jacob | MS | Project Coordinator |
| Grilli, Matthew | PhD | PI |
| Haaheim, Lisbeth | BS | Project Coordinator |

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|---|---|---|
| Hall, JD | MS | PhD Candidate |
| Hay, Meredith | PhD | PI (25% effort on parent grant) |
| Holguin, Gabriel | MA | Graduate student, Neuropixels recording in behaving rats |
| Hoscheidt, Siobhan | PhD | Investigator, Psychology |
| Hovhannisyan, Mariam | MA | Co-I |
| Hutchinson, Elizabeth | PhD | Assistant Professor, BME, UA |
| Irwin, Kristina | BS | Research Manager, Psychology |
| Jebahi, Fatima | MS | MS, PhD student |
| Jessup, Cortney | MPA | Research Coordinator |
| Johnson, Daniela | BA | Undergraduate Research Assistant |
| Kalya, Anantharam | MD | Physician |
| Kielar, Aneta | PhD | Project PI, Department of Speech, Language and Hearing Sciences |
| Leslie, Angel | MS | Pharmacology Doctoral Student, College of Medicine -Tucson |
| Liiu, Yilin | PhD | Postdoc Researcher |
| Matijevic, Stephanie | PhD | Postdoc, Psychology |
| Maxwell, Raeven | BS | Coordinator |
| Mi, Yashi | PhD | Research scientist |
| Murphy, Devin | MS | Graduate Research Assistant, BME, UA |
| Murray, Diana | BS | Clinical Research Coordinator |
| Mushtaq, Raza | MD | Consultant (radiology expert) |
| Nickels, Katlyn | PhD | Postdoctoral Fellow (Part Time) |
| Oskouie, Suzanne | MD | Physician |
| Palmer, Justin | MS | Graduate Student, Psychology |
| Pires, Paulo | PhD | Associate Professor, Physiology, UA |
| Porter, Lydia | BS | Undergraduate Researcher |
| Reyes-Reyes, Elsa | PhD | Research Assistant Professor, Medicine |
| Rogers, Kathleen | PhD | Principal Investigator |
| Ryan, Lee | PhD | PI, Psychology, Neurology, Neuroscience Program, Evelyn F. McKnight Brain Institute |
| Sanchez, Darianne | BSc | Graduate Assistant |
| Schrag, Cindy | BS | Coordinator |
| Serna, Mauricio | BS | Technician, Data collection, Data post-processing |
| Siu, Hannah | BS | Project Coordinator |
| Snider, Justin | PhD | Assistant Research Professor |

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|---|---|---|
| | | Co-director UACC Analytical Chemistry Shared Resource |
| Song, Hyun | MA | Graduate Research Assistant |
| Srivathsa, Sahana V. | MA | Graduate student, data collection, surgeries, analaysis |
| Su, Judith | PhD | PI, Director, Little Sensor Lab |
| Sundman, Mark | PhD | Research Scientist |
| Sweitzer, Nancy K | MD, PhD | Physician |
| Trial, Michael | BS | Research Technician III, Health Sciences and Brain Science |
| Trouard, Theodore | PhD | Co-I, Professor Emeritus, BME, UA |
| Vishwanath, Abhilasha | MA | Graduate student, Data collection, surgeries, analysis |
| Weinkauf, Craig | MD, PhD | Co-I |
| Winter, Gabriel | MA | Graduate student, Transgenic AD colony management, behavioral assessment |
| Wiskoski, Haley | MSc | Graduate Assistant |
| Yin, Fei | PhD | PI |

# UNIVERSITY OF ARIZONA
# COLLEGE OF MEDICINE – PHOENIX

The University of Arizona (UA) has a strong history of academic and medical excellence in the state of Arizona, governed by the Arizona Board of Regents. Two medical school campuses have been established, one located in Tucson at the Arizona Health Sciences Center and University Medical Center, and one located in Phoenix on the Phoenix Bioscience Core (PBC). The UA College of Medicine – Phoenix shares the PBC campus with the UA Coit College of Pharmacy, UA Zuckerman College of Public Health, UA Eller College of Management, and several allied health programs from Northern Arizona University, Arizona State University, the Translational Genomics Research Institute, and the Phoenix VA Research Service. Through these many colleges and institutions, the UA College of Medicine – Phoenix is uniquely positioned to accelerate the biomedical and economic engines in Phoenix and the State by leveraging vital relationships with key clinical and community partners.

The UA College of Medicine – Phoenix mission is to inspire and train exemplary physicians, scientists, and leaders to optimize health and health care in Arizona and beyond. The UA College of Medicine – Phoenix was founded in 2007 as a full, four-year medical program. It was granted full independent accreditation by the Liaison Committee of Medical Education (LCME) in June 2017. At its new class size, the program matriculates 120 new allopathic doctors each year. The UA College of Medicine – Phoenix continues to expand and grow as it also provides graduate training opportunities through the Clinical Translation Science Program. This program offers MS and PhD and combined MD/PhD and MD/MPH degrees.

The UA College of Medicine – Phoenix commits to life-long learning and critical thinking for all trainees, staff, and faculty. One example of this commitment is the requirement for all medical students to complete a Scholarly Research Project over their four years of medical training. Students are paired with physicians and translational scientists to complete projects that culminate in a thesis as part of the graduation requirements.

As part of the overall mission of the university, UA College of Medicine – Phoenix has developed and continues to reinforce cooperative agreements, partnerships, and collaborations with local institutions. Some examples include the development of the Neurotrauma & Social Impact research team, a collaboration between the UA College of Medicine – Phoenix and Phoenix VA Health Care System. The team sets the goal to be the premiere destination for neurotrauma research, training, and collaboration. More recently, this program has engaged with partners from the Maricopa County Attorney's Office, Mesa and Tempe Police Departments, The Sojourner Center, and The CACTIS Foundation to establish the Maricopa County Collaboration on Concussion in Domestic Violence (MC3DV). Primary research directions for the program include inflammation, rehabilitation, and practical therapies for traumatic brain injury as a causative factor in challenging healthy aging and promoting neurodegenerative disease.

## UNIVERSITY OF ARIZONA
## COLLEGE OF MEDICINE – PHOENIX

| Name (last, first) | Degree | Role on project |
|---|---|---|
| Giordano, Katherine R. | BS | CTS Graduate student |
| Griffiths, Daniel R. | BS | Research Specialist, Senior |
| Leighty, Connor R. | BS | CTS Masters student |
| Lifshitz, Jonathan | PhD | Principal Investigator, Research Professor |
| Mahrer, Callie | MS | CTS Graduate student |
| McQueen, Kyli A. | BS | Research technician |
| Tallent, Bret R. | Latg | Laboratory manager |


# PROJECT PROGRESS REPORTS

# ARIZONA STATE UNIVERSITY
# PROJECT PROGRESS REPORTS

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Evaluation of Clinically-Used Progestogens on Cognition During the Transition to Menopause in the Rat.** Heather Bimonte-Nelson, PhD (President's Professor, Psychology Department), Juliana Kling, MD, MPH. Arizona State University; Mayo Clinic Arizona; Mayo Clinic Alix School of Medicine, Arizona Campus; Arizona Alzheimer's Consortium.

**Specific Aims:**

The specific aim of this proposal is to systematically determine the effects of MPA, micronized progesterone, and progesterone on cognition during the menopausal transition.

**Background and Significance:**

The transition to menopause can last as long as 10 years, and involves ovarian follicular depletion (Burger et al., 2008; Harlow & Paramsothy, 2011). During perimenopause, progestogens, which include both progesterone and its synthetic analogs, known as progestins, are prescribed to women to combat heavy uterine bleeding as well as other symptoms. Progesterone and some of its metabolites have been shown to be neuroprotective in counteracting damage due to ischemic stroke, traumatic brain injury, and experimentally-induced excitotoxicity in the hippocampus in rodent models (Ciriza, Azcoitia, & Garcia-Segura, 2004; Shear et al., 2002; Wali et al., 2014). Progesterone administration has mixed effects on cognition in healthy animals that do not have brain injury. In young, middle-aged, and aged ovariectomized (Ovx, whereby the ovaries are surgically removed) mice, acute progesterone treatment improved non-spatial memory and memory consolidation on an object recognition task, compared to vehicle controls (Harburger et al., 2008; Lewis, Orr, & Frick, 2008). In contrast, our laboratory has demonstrated that chronic progesterone administration in middle-aged Ovx rats impairs spatial working memory (Braden et al., 2015). Medroxyprogesterone acetate (MPA), an acetylated pregnane derivative of progesterone (Stanczyk, 2003), is administered in women during the menopausal transition to alleviate undesired physiological symptoms, such as heavy uterine bleeding, and is also available in the clinic as birth control under the brand name DepoProvera (Depo Provera Prescribing Information, 2006). There are limited evaluations of MPA on the brain and cognition. In our and other laboratories, MPA alone has been shown to have negative effects on spatial memory in Ovx rats compared to vehicle controls (Braden et al., 2017, 2011, 2010) as well as on a novelty memory task in young ovary-intact rats (Okojie & Oyekunle, 2014). The MPA- induced cognitive impairment is likely non-reversible, as Ovx rats tested four months after the cessation of short-term MPA treatment still demonstrated cognitive impairment compared to age- matched vehicle controls (Braden et al., 2011). Women can also be prescribed micronized progesterone to combat physiological symptoms associated with perimenopause (Stute et al., 2016; Gillet et al., 1994). Micronized progesterone is identical in chemical structure to progesterone and presumably acts upon similar neurobiological pathways, although the literature is unclear if micronization impacts the pharmacokinetics and/or pharmacodynamics of progesterone, and no work has evaluated its preclinical mnemonic effects with menopause (De Lignières, 1999; Maxson & Hargrove, 1985).
Menopause-related preclinical progestogen investigations of cognition have been limited thus far to models of surgical menopause via Ovx, which removes the primary source for ovarian hormones, yielding an abrupt, drastic decrease in circulating ovarian hormone levels. However, over 80% of women do not undergo surgical menopause, and instead undergo a naturally occurring transitional menopause during which there is a loss of ovarian follicular function (NAMS, 2014). The 4-vinylcyclohexene diepoxide (VCD) rodent model is used to induce ovarian follicular depletion of primary and primordial follicles via accelerated atresia, and produces a circulating ovarian hormone profile which is more similar to a woman undergoing transitional menopause compared to the Ovx rodent model (Acosta et al., 2010; Hoyer et al., 2001; Kao, Sipes, & Hoyer,

1999; Koebele et al., 2017; Mayer et al., 2004). Further, the VCD model allows for targeted timing of the menopause transition since VCD-induced follicular depletion occurs over time, while Ovx is an all-or-nothing, abrupt phenomenon. The Ovx model lacks a transition stage, while with the VCD model, hormones can be administered during the transition to menopause. Assessing exogenous progestogen administration in the VCD model of follicular depletion will help determine these clinically relevant hormone interactions and their effects on cognition. As such, the specific aim of this proposal is to systematically determine the effects of MPA, micronized progesterone, and progesterone on cognition during the menopausal transition.

**Experimental Design and Methods:**

Fifty female, virgin, Fischer-344-CDF rats will be obtained from the National Institute on Aging (NIA), Harlan Laboratories (Indianapolis, IN, USA). Animals will be pair-housed and fed ad libitum for two weeks before the study begins. Rats will be placed on a 12-hour on/off light-dark cycle, and will be treated in compliance with the Arizona State University Institutional Animal Care and Use Committee protocol. All procedures will adhere to the standards provided by the National Institutes of Health. Rats will be administered VCD (160mg/kg/day, n=40) via intraperitoneal injection in accordance with published protocols (Acosta et al., 2009, 2010; Koebele et al., 2017). Rats will receive either progesterone, micronized progesterone, medroxyprogesterone acetate, or vehicle, and will then receive a battery of learning and memory tasks. In addition, the control visible platform task will be given to confirm motoric and visual procedural components of a water-escape maze task.

**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 grant to NIH.

**Year End Progress Summary:**

Rats were ordered immediately as proposed. The VCD was initiated to experimentally induce ovarian follicular depletion, and progestogens were administered. Rodent behavior testing has been completed with the behavioral spatial working and reference memory battery as proposed. We have scored all behavioral data and are analyzing final results currently. Thus far, preliminary results indicate that the progestogens have impacts on spatial cognition, with comparatively divergent effects depending on memory type and the specific type of progestogen.

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Investigating an African American-Specific APOE Genetic Variant Using HiPSCs.** David Brafman, PhD. School of Biological and Health Systems Engineering, Arizona State University; Arizona Alzheimer's Consortium.

**Background and Significance**:
The lifetime risk of developing Alzheimer's disease (AD) is almost two time greater in African Americans as compared to European Americans. While it is speculated that these differences arise from a combination of environmental and genetic factors, the underlying mechanisms of this health disparity in disease risk is poorly understood and significantly understudied. Of these genetic risk factors, polymorphism in the Apolipoprotein E (APOE) gene, a lipoprotein transporter involved in cholesterol metabolism, is the strongest and most prevalent. In the central nervous system, APOE is generated and secreted principally by astrocytes and functions to transport cholesterol and other lipids to neurons. As such, APOE plays important roles as it relates to neuronal growth, synaptic plasticity, and membrane repair. In European Americans, with respect to AD, compared to individuals homozygous for the APOE3 allele, heterozygosity for the E4 allele increases AD risk by 3 fold, and homozygosity for the E4 allele increases risk over 10 fold. Conversely, individuals with the E2 allele are 40 percent less likely to develop AD. Along similar lines, African Americans have a higher prevalence of APOE4 and its presence is thought to contribute, in part, to higher levels of AD in African-ancestry groups. More recently, a missense variant in APOE, APOE R145C, was identified as conferring select risk in populations of African descent, including African Americans. This variant which is common in individuals of African ancestry (MAF = 4%) but rare in Europeans (MAF < 0.01%) has been previously linked to type III hyperlipoproteinemia (HLP). Mechanistically, the APOE R145C variant has a lower binding affinity to heparin sulfate proteoglycans (HSPG), which play roles in the cellular uptake of Aβ and tau. Moving forward, precise understanding of the molecular mechanisms by which the APOE R145C variant mitigates AD onset and progression will be critical for developing targeted therapeutic interventions for the high risk African American populations.

**Specific Aims:**
We and others have used human induced pluripotent stem cell (hiPSC)-based models, which are highly complementary to existing animal models, to study AD in a simplified and accessible system. However, the analysis of the phenotypic effects of specific risk factors, such as those in the APOE locus, has been confounded by the genetic and epigenetic differences inherent in the individual hiPSC lines derived from distinct patients. As such, the use of isogenic hiPSC lines with identical genetic backgrounds that only differ with respect to individual variants has become the gold standard in modeling and analyzing the effects of AD-related risk factors. We recently reported the development of a series of methods that employ a transient reporter for editing enrichment (TREE) which allows for the generation of isogenic hiPSC lines with clonal homozygous editing efficiencies approaching 90%. In this proposal, we will utilize these TREE-based approaches to introduce the APOE R145C mutations into isogenic hiPSCs from both non-demented control (NDC) and AD patients. In turn, we will differentiate these hiPSC lines into neuronal, astrocytic, and microglia cultures to address the following hypothesis-testing questions: (1) Does the presence of the APOE R145C variant modulate disease-related phenotypes in a hiPSC-based system and across multiple FAD-related mutations? (2) Is the risk-inducing effects of APOE R145C mediated through cell-autonomous or non-autonomous mechanisms? (3) Does APOE R145C exert its risk-modifying effects on the on the same pathologically-related molecular processes and pathways as other APOE isoforms? To that end we propose the following specific aims:

**Specific Aim 1:** Employ a TREE-based genome editing approach to introduce APOE R145C into isogenic hiPSC lines.

**Specific Aim 2:** Examine the specific effect of APOE R145C on the modulation of AD-related phenotypes and molecular processes.

**Preliminary Data, Experimental Design and Methods:**

***Generation of pure populations of functionally mature hiPSC-derived cortical neurons and astrocytes.*** Using a combination of directed differentiation protocols and magnetic-activated cell sorting (MACS) strategies we have developed methods for the large-scale generation of hiPSC-derived neurons, astrocytes, and microglia.

***Rapid and highly efficient generation of isogenic hiPSC lines.*** As detailed most recently in our Nature Protocols and Stem Cell Reports publications we have developed a series of methods that employ transient reporters of editing enrichment (TREE) to facilitate highly efficient (>80%) single base pair editing of human cells at precise genomic loci. In addition, these TREE-based approaches provide for the generation of KO hiPSC lines without the introduction of deleterious DSBs. Critically, our TREE-based approaches allows us to generate isogenic hiPSC lines with unparalleled efficiency and uniquely position us to study APOE independent of genomic variability.

***Using human induced pluripotent stem cells (hiPSCs) to investigate the mechanisms by which various genetic factors modulates Alzheimer's disease (AD) risk.*** We have used TREE-based gene editing methods to introduce genetic risk factors into isogenic hiPSCs derived from a variety non-demented control (NDC) and AD patients. Overall, these experiments demonstrate our ability to use isogenic hiPSC lines to investigate the mechanisms by which various genetic factors modulates AD risk.

**Experimental Designs and Methods:**

**Specific Aim 1.** We have previously generated APOE isogenic series (homo- and heterozygous for E4, E3, E2, KO) in hiPSCs with familial AD (FAD) mutations in APP (APPdp) and PSEN1 (PSEN1A246E) as well as those from sporadic AD (SAD) and non-demented control (NDC) patients. Thus, since we have shown that introduction of APOE variants into these lines modulates disease-related phenotypes, we contend that modulation of these phenotypes by introduction of APOE R145C genes will be readily observed. For this proposal, we will further modify these lines by using PINE-TREE based genome engineering to introduce the APOE R145C variant. It should be noted that we focus on introducing this variant into the isogenic lines with APOE E3/E4 genotype as the APOE R145C variant was associated with the highest level of AD risk in individuals with that genotype. Importantly, these hiPSC lines are equal in terms of their representation from male and female patients, which is important given the gender-based differences in AD risk.

**Specific Aim 2.** Although astrocytes are the major source of APOE production in brains, disease-related phenotypes are mediated by the interactions of these secreted proteins with neurons and microglia. As it relates to amyloid-associated processes, neurons act as the primary producers of Aβ from the amyloidogenic processing of amyloid precursor protein whereas non-neuronal cells, such as astrocytes and microglia, facilitate its clearance. The imbalance in these processes is thought to be a primary driver of elevated extracellular Aβ levels that drive the amyloid cascade. Thus, in Sub-Aim 2.1 we will examine the effect of APOE R145C on neuronal processing of APP in the context of both purified populations of neurons as well as co-cultures of neurons and astrocytes in defined ratios. In parallel, in Sub-Aim 2.2 we examine the mechanisms by which APOE R145C modulates Aβ uptake in purified cultures of astrocytes and microglia as well as microglia cultures supplemented with astrocyte-conditioned medium obtained from the same isogenic line. With respect to tau-related phenotypes, in Sub-Aims 2.3 and 2.4, we will not only

examine tau-related phenotypes in monotypic cultures of purified neurons but also (i) co-cultures of neurons and astrocytes and (ii) co-cultures of neurons and microglia.

**Proposed One-Year and Long-Term Outcomes:**

Overall, this hypothesis-testing and - generating proposal will provide more definitive relationships between APOE R145C and AD- related phenotypes. 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 specific African American- associated APOE variants accelerate AD onset. This resource-generating (Specific Aim 1) and hypothesis-testing (Specific Aim 2) proposal will enable us to determine the extent to which APOE modulates specific AD-related phenotypes. Although the proposed studies will not interrogate all of the hypothesized mechanisms by which APOE R145C modulates 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.

**Year End Progress Summary:**

1. Generation of isogenic hiPSCs. Over the past year, we have built upon this work to establish a new TREE-based method entitled prime-induced nucleotide engineering using a transient reporter for editing enrichment (PINE-TREE) to detect and report upon prime editing activity with a cell. Moreover, we demonstrated at several AD-related loci and across various types of genomic modifications (i.e., base substitutions, insertions, deletions) that PINE-TREE allows for the real-time identification and purification of edited cell populations. We employed PINE-TREE to modify hPSCs resulting in editing efficiencies significantly exceeding those using typical enrichment strategies. Finally, we demonstrated that PINE-TREE provides for the efficient generation of clonal isogenic hPSCs at loci that are difficult to edit using traditional reporter of transfection (RoT)-based PE enrichment techniques. Overall, PINE-TREE is a highly adaptable and easily implemented method that will greatly enhance the use of PE technologies for numerous in vitro applications. Moving forward, we are using PINE-TREE for the highly efficient introduction of the variant into isogenic hiPSCs.
2. Role of APOE genotype in microglia function. We have refined and developed protocols result in the large-scale generation a highly pure population of microglia (>80% TREM2 / IBA1- postive) with cells morphologically distinct from monocytes and macrophages. More specifically, these microglia-like cells resemble human fetal and adult microglia as they display an axial bipolar morphology and express high levels of canonical microglial markers such as TREM2 and IBA1. Functionally, these microglia-like cells also display the ability to rapidly, uptake fluorescently tagged Aβ42 as measured by real-time fluorescent microscopy. Together, 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. Such analysis will enable us to determine the extent by which APOE R145C modulates AD-related phenotypes in a cell-specific manner.
3. Submission of grants to NIA. Using the preliminary data generated over the past year, we have submitted an R21 to the NIA that scored at the 7th percentile and is recommended for funding.

# ARIZONA ALZHEIMER'S CONSORTIUM
# 2023-2024 Scientific Progress Report

**Age and Chronic Stress Interactions on Memory and Anxiety in Female Rats.** Cheryl D. Conrad, PhD, Thu Huynh, PhD. Arizona State University; Midwestern University; Arizona Alzheimer's Consortium.

## Specific Aims:

The specific aim of this project is to test whether a chronic unpredictable stressor has lasting effects on exacerbating memory decline in female rats as they age.

## Background and Significance:

Major affective disorder (MDD) affects millions of people worldwide, with MDD being the highest ranked mental disorder for years lived with disability in the U.S. MDD involves altered mood and/or loss of interest in pleasurable activities with women having a two-fold greater chance of developing MDD than men. Moreover, women experience a heightened risk for developing MDD during middle-age, when ovarian hormone levels unpredictably fluctuate and eventually wane. Stress is a potent trigger that can enhance mental dysfunction and even accelerate MDD onset and/or severity with age. Other symptoms that can be variably expressed with MDD include cognitive dysfunction, a newly recognized MDD symptom by the American Psychological Association and listed in the recent version of the Diagnostic and Statistical Manual of Mental Disorders, and anxiety, both of which tend to be highly co-morbidly expressed by women. Unfortunately, much of the science undertaken to study MDD was based upon work using males and in young adults. One goal of the undertaken work was to include females and middle-age, a critical demographic that is susceptible to MDD, but greatly understudied.

Understanding MDD is complicated by other factors and can include the heterogenous of the disorder and the likelihood of many etiologies. Two individuals could be diagnosed with MDD but express non-overlapping symptomology: one can be suicidal, lose weight, and express sleeplessness, while the other might be socially withdrawn, unable to concentrate and show high anxiety. Further, we are far from providing personalized treatment for each person suffering from MDD: Patients are often prescribed antidepressants and if treatment fails, the patient is tested on a new set of medications until something works. Moreover, 2/3 of patients respond to medication and of these many will relapse. Consequently, preclinical studies investigating the biological causes of MDD are essential to understand and successfully treat the disorder.

The goal of this work was to investigate a preclinical model of MDD using chronic stress in rats to learn how symptoms and brain signaling processes change with time between young adults and middle-aged female rats. We targeted females because they are understudied and show greater MDD development than males. The two ages investigated were young adult and middle-age so that we can determine whether middle aged females are particularly vulnerable than their younger counterparts and identify biological determinants that make them vulnerable. One symptom investigated tapped into cognitive fog and focused on two similar but distinctive cognitive tasks. One relies upon the hippocampus and the other taps into the prefrontal cortex, brain structures that are implicated in MDD. The other focused on anxiety because it is highly comorbidly expressed in women with MDD. Altogether, we targeted intracellular signaling processes in the hippocampus and prefrontal cortex to determine how chronic stress, age, and timing could potentially alter these processes with the goal of manipulating these in the future to treat MDD.

## Preliminary Data, Experimental Design and Methods:

The design of our study used two independent variables (Age and chronic stress) and assessed dependent variables from 1) behavior using three different tasks (Morris water maze = MWM,

radial arm water maze = RAWM, elevated plus maze = EPM) and 2) the brain targeting signaling proteins from four different brain regions (hippocampus, prefrontal cortex, amygdala, and cerebellum). The two ages were young, adult (5-months) and middle-aged (14-months) female rats. The three chronic stress manipulations were control (CON, i.e., not chronically stressed), rats that were tested during chronic stress or "current" (STR-C), and rats that were tested after chronic stress ended and was in the 'past" (STR-P). For the dependent measures, the MWM helped to assess hippocampal-dependent cognition, the RAWM helped to assess prefrontal cortex-dependent cognition, and the EPM helped to assess anxiety profile. The four brain regions were extracted for assessing signaling pathways. Our power analysis revealed that we needed n=12 rats/group, which would be (12rats/group x 6 groups = 72 rats total). Due to the number of rats we needed to test, we had to split the testing into two cohorts with one set of rats tested in the fall 2023 and the other set tested in the spring 2024. For each cohort, we ensured that both ages and all three stress conditions were included.

**Proposed One-Year and Long-Term Outcomes:**

Behavioral testing will be completed by the end of the 1-year project period. Western blots will be performed as soon as the brain tissue is collected. Data quantification and analysis will occur during the summer 2024 and we will submit a manuscript and grant proposal in the spring 2025.

**Year End Progress Summary:**

We were able to complete the behavioral testing as proposed by May 2, 2024. One of the challenges we encountered involved sharing the use of the RAWM testing room. We needed to work with our colleagues to shift and arrange schedules so that the timeline for both cohorts of rats would be consistent and yet work with similar needs of our colleagues. Consequently, our next proposal included a new RAWM setup, which will greatly offset the burden of multiple investigators trying to use the same testing room. We have the brain tissue frozen and plan to run assays on the tissue in the fall. A current challenge is that the graduate student who ran this study is no longer in the laboratory. I will be looking for a new student who can help with quantifying the brain data and the MWM data, the latter of which requires re-tracking to ensure that the tracking focused on the rats and not extraneous cues. The last time retracking occurred, the graduate student took approximately 80 hours to extract the data over a semester. Consequently, the updated timeline is as follows:

1. Fall 2024, extract MWM data and analyze it
2. Fall 2024 and Spring 2025, run western blots on brain tissue
3. Submit a manuscript from these data in summer/fall 2025

In terms of grant proposals, we received funding previously and are on track with submitting a grant proposal to the National Institute on Aging in October 2024.

Another update is that during the month of May and June when I received a salary from AAC, I re-analyzed data from another study with middle-aged, ovariectomized female rats that were given stress levels of the stress hormone, corticosterone, or vehicle. Depressive-like behavior can be generated by chronic stress or by using daily exposure to corticosterone. We report new findings that chronic corticosterone produced a depressive-like state in ovariectomized middle-aged females and that this depressive state significantly and positively correlated with anxiety profile. This outcome fits our prediction, and this will be published in Hormones and Behavior (accepted on July 3, 2024).

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**CarePRO Virtual Long Term Care (LTC): Video-conference Delivery of an Evidence-based Intervention.** David W. Coon, PhD, Janet Pohl, PhD, RN. Arizona State University; Arizona Alzheimer's Consortium.

**Specific Aims:**

a) Finalize intervention protocol for video-conference (Zoom) delivery of CarePRO Virtual Long Term Care; (CarePRO Virtual LTC, an evidence-based intervention) using (1) focus group data previously collected with family members and providers who assist this population; and (2) pre-pilot experience prior to the COVID-19 pandemic delivering CarePRO LTC face-to-face and in-person.

b) Implement revised screening and interview protocol based on data in Specific Aim "a".

c) Conduct a single arm pre-post study using the CarePRO Virtual LTC intervention with up to 25 participants through a pilot feasibility and acceptability trial.

d) Use appropriate statistical analyses to provide descriptives that characterize the sample and further examine CarePRO Virtual LTC feasibility and acceptability as well as inferences to describe the impact of the intervention.

e) Disseminate findings through presentations at national conferences such as the Gerontological Society of America and the American Psychological Association.

**Background and Significance:**

In 2022, approximately 6.5 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 7.2 million by 2025.1 Arizona at 33.3% is the state with the largest projected percentage increase from 2020 to 2025. The growing numbers of older adults and people living with dementia are driving the need for a variety of residential care facilities that cover the spectrum of care needs. Recent estimates indicate people living with ADRD make up 34% of residents in residential care facilities including assisted living communities and 48% of nursing home residents with 61% of these residents having at least moderate cognitive impairment (1,2). Only a small minority live in dementia special care units where care and related policies are in place to meet their needs (3). Forthcoming increases in the prevalence of ADRD will also have a marked impact on family caregivers. Family caregiving comes with economic, psychosocial, and health costs, as caregivers can experience job and financial loss, mental health concerns, poorer health, and social withdrawal and isolation (1). It is important to note that caregiving does not end with placement; and while research findings are mixed, many studies suggest that caregiver stress and distress remains either unchanged or actually increases after placement.(4-6).

To date, interventions for caregivers who placed their loved ones have not proven to be effective in reducing depression, anxiety, or other negative mental health outcomes, although in a few cases an intervention has helped ameliorate guilt, grief, and stress appraisal (7-9). CarePRO Virtual LTC, 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 (9) and expand its reach to caregivers of people with ADRD living in long term care. It does so in part by providing via Zoom interactive group sessions for caregivers that deliver the original intervention's proven skill-building strategies through trained co-leaders in a group setting that also helps 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) (9-10). During Zoom-based coach calls, CarePRO Virtual LTC 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 (10).

**Proposed One-Year and Long-Term Outcomes:**

The proposed short-term outcomes are described as outputs 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 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 in Spring of 2025, depending on the pilot project's findings.

**Year End Progress Summary:**

Specific aims a and b were completed with the remainder still in progress. Additional participants are still participating in the intervention, so additional analyses and dissemination activities are forthcoming. Based on prior focus group findings, we re-ordered the sessions including moving communication skills and unhelpful thinking strategies earlier in the intervention; the loved ones of LTC family caregivers are in more advanced stages of dementia leading to different stressors and related distress with the need for more relevant in-session examples and skills-based exercises; many family caregivers expected to have reduced stress after placement, but placement comes with new stressors and related distress, often with much higher levels of reported guilt (e.g., placement is seen as a failure), social isolation, and loneliness; new roles emerged including patient advocate with facility administration and staff as well as advocate addressing family members who do not support and/or understand placement; role confusion emerges related to issues of control around prior care responsibilities; challenges to re-engaging with their lives outside of the caregiving role present new opportunities for social interaction and pleasant activities; staff training and re-training given high staff turnover and the need to educate staff about their loved ones; and additional focus emerged on End-of-Life issues and relevant care values.

Additional intervention groups are underway with an emphasis on increasing diversity of participants. The sample to date is similar to findings in the literature with the majority of caregivers self-identifying as non-Hispanic white; female (92.9%); adult child (71.4%); and a college graduate (78.6%). Caregivers ranged from 19 to 81 (average 64.6 years) with care recipients being a good deal older ranging in age from 63 to 92 (average 82.9 years). Care recipients were also non-Hispanic white but only 28.5% were college graduates. All caregivers reported visiting their loved ones at least once a week (64.3%) if not once a day (35.7%) and given that the majority were adult children, less than half (42.9%) of the care recipients lived with them prior to placement. Care recipients had been in long term care for an average of 1 year and 8 months with placement ranging from 1 month to 3.5 years. Preliminary results show solid feasibility and acceptability with no dropouts to date and 100% of participants completing all sessions and coach calls. In terms of perception of benefit, 100% of caregivers reported: overall benefit from their participation in CarePRO LTC; better understanding of memory loss and its effects on people; more confidence in dealing with their loved one's memory problems. They also reported CarePRO LTC made their lives easier; enhanced their ability to care for their loved one; and improved their loved one's life. The percentage of caregivers who reported a great deal of improvement for these outcomes ranged from 100% for overall benefit to 83% for all other outcomes except improving their loved one's life. With regard to the latter, only 17% reported a great deal of improvement and 83% reported CarePRO LTC helped some—this is not surprising given the ongoing decline of their loved one. Additional results show that all caregivers (100%) increased their overall confidence in providing care for their loved ones and increased their engagement in leisure time activities; 66.6% of caregivers reported improvements in mood and positive aspects of caregiving; and 50%

stated increased satisfaction from their support systems. Pre-post analyses for key outcomes will be conducted after the final group of participants complete the intervention.

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# ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Arizona Alzheimer's Consortium Public Conference.** David W. Coon, PhD. Arizona State University; Arizona Alzheimer's Consortium.

**Specific Aims:**

a) Reinstitute the Arizona Alzheimer's Consortium Public Conference.
b) Collaborate across institutional partners to help identify speakers and market the conference to the public.
c) Gather data to gather demographic characteristics of the attendees and evaluate conference participant perceptions 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 2023, the Alzheimer's Association reported that approximately 6.9 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 7.2 million by 2025. In 2022, Arizona at 33.3% was projected to be the state with the largest projected percentage increase from 2020 to 2025. In addition to those living with the disease, informal caregivers are impacted by AD with more than 11 million people in the U.S. providing unpaid care for a family member or friend with AD, a contribution to the country valued at almost $350 billion. The non-match funds will be used to reinstitute the Arizona Alzheimer's Consortium's (AAC) statewide public conference reaching out to 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 the Memorial Union on Arizona State University's Tempe campus on Saturday April 27, 2024 (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 included representatives from BAI Family and Community Services, AZDHS, AZDES-DAAS, AARP, the Hope Network, and the Desert Southwest Chapter of the Alzheimer's Association.

The program provided substantive but relatively short talks of 15 minutes delivered by experts in new drug treatments, blood tests for AD, brain and body donation, risk reduction through exercise, leveraging MindCrowd and the Precision Aging Network to personalizing approaches to brain aging, care planning interventions for people with early stage AD and family caregivers, and how and why to get involved in research. The day ended with a panel discussion with expert providers from healthcare and community services.

This is the first post-COVID AAC Public Conference and similar to other free conferences where registration (338 registrants) was much higher than those that attended (155 attendees). While feedback from attendees supported the premise of providing a time to meet the needs of working families, other feedback suggested that better directions and mapping of parking and pathways to the Memorial Union were needed. Eighty-one attendees (52.3%) filled out the post-conference survey with the majority self-reporting as women (73.8%), college graduates (54%),

and non-Hispanic White (81.3%) with largest ethnic/racial minority being Hispanic/Latino (10%). Ages ranged from 12 to 84 years of age (average age = 55.2 years old).

The vast majority of people at the conference were first-time attendees (72.8%), with only 18.5% 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; and only 14% having participated in a research study about family caregiving or care planning sponsored by the same entities. 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. Almost all of those completing the survey (97.5%) stated they were able to better understand the progress being made in Arizona regarding the early detection tracking and treatment or retention of AD. Most of the participants heard about the conference through a relative or friend (33%) followed by email directly from the AAC (19%), and email from healthcare or other community-based organizations (14%). Over 92% agreed that the conference met their expectations, were satisfied by the conference, would recommend it to others, learned something they could use, and thought registering for the conference was simple. These positive ratings are likely even higher as the 4.9% who marked "strongly disagree" to these questions wrote positive comments about the conference and may have inadvertently checked the wrong response.

# ARIZONA ALZHEIMER'S CONSORTIUM
# 2023-2024 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.

## Background and Significance:

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 new brand package will be incorporated into both websites azalz.org and azadrc.org and also funnel participants, the general public, and scientists to our overall outreach efforts. These funds will help support ongoing updates to the AAC website to maintain the latest website standards (including security standards).

## Year-End Progress Summary:

The team advanced AAC Website updates 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: rollout of branding and design guidelines across web and video/print media, with ongoing refinements based on technology and platform / user experience updates (backend database functions, web security, and multi-platform optimization); continued deployment of our a new logo honoring diversity, heritage, history, outreach, and our extremely broad and deep scientific platform; integrate this logo 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; 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 186 minutes (3.1 hours) of new content in addition to 981 minutes (16.35 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 achieved 14.4K impressions (meaning at least partial views) from July 1, 2023 – June 30, 2024. Additional content that is currently under review and being published to the websites includes recent presentations from our scientists; more than 100 new graphics and images sourced for use; and new drone footage of our communities to emphasize the far-reaching effect of our multi-site statewide presence. Video footage and interviews from the upcoming 2023 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 engaging our underserved Latino/Hispanic community. Content is also developed and made available for repurpose into additional social media and traditional media campaigns. This year we produced “remote” packages via Zoom allowing scientists and researchers to pre-record informative presentations for distribution at our AAC Public conference with 338 in-person registrants and then to be packaged for distribution through our online video channels. Video footage and interviews from the upcoming 2024 AAC Scientific Conference will be published as well.

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 our underserved 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
## 2023-2024 Scientific Progress Report

**Resilience Promoting Social Networks Among Caregivers of Persons Living with Dementia in Arizona**. Aaron Guest, PhD, MSW, Allie Peckham, PhD, MSW, Keenan Pituch, PhD, Alzheimer's Prevention Registry. Arizona State University; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

**Specific Aims:**

1) We are determining the effects of time as a caregiver on social network attributes and perceived reliance on network members.
2) We are examining the relationship between caregivers' social network compositions and caregiver resilience, well-being, and burden.

**Background and Significance:**

Caregivers of people living with dementia (PLWD) report lower levels of perceived life satisfaction and higher rates of depression and anxiety than those caring for individuals not living with Alzheimer's Disease or Related Dementia (ADRD), all of which impact engagement (1,2). Dementia caregivers are more likely to self-report declining health, experience burden, and missed time at work, and are also more likely to use emergency-based support (3,4). This study aims to develop new insights into the attributes of ADRD caregiver social networks and test the feasibility of spatial social network (SSN) data collection and understand the SSN compositions of dementia caregivers (6,7). Understanding how social networks are used throughout the caregiving experience for ADRD caregivers is critical to identifying interventions that build supportive networks that promote well-being for ADRD caregivers (5,9).

**Preliminary Data, Experimental Design and Methods:**

We are employing a mixed-methods, exploratory study that involves a structured telephone interview in year one with caregivers of persons living with dementia (PLWD). Participants are engaging in a 60-minute structured interview in Year 1 (n=100) with a planned 45 to 60-minute in-depth interview in Year 2 (n=75). In year 1, participants are asked about caregiver and care recipient demographics, caregiver background, caregiver stress, resilience, well-being, and egocentric social network data. Network composition attributes, such as tie strength, the function of the relationship, and reliance on network members, are also being assessed.

For the preliminary analysis, we looked at 73 individuals (75% white [13.7% Black, African-American], 84.9% female, with 43.1% having outside employment, and 38.4% being the spouse of the person they are providing care for, followed by 20.5% being the parent, and 20.5% being the child of the care recipient). Social network satisfaction, as measured by the three-item Social Network Satisfaction Scale, was significantly negatively associated with scores on the Zarit Caregiver Scale (-.291 to -.334 with p-values between .022 and <.001) and the UCLA Loneliness Scale (-.482 to -.661, p<.001), as well as positively associated with the Social Wellbeing Index Score (.454-.747, p<.001), and Friborg resilience subscales of perception of self/future (.362-.425, p<.001 - .03) and social resources (.450-.544, p<.001) at the .01 level. In summary, higher social network satisfaction is linked to lower caregiver burden and loneliness, as well as higher social well-being and resilience. At the .05 level, there was a significant positive association with the resilience subscale for family cohesion (.276 p=.025 for questions 1&3 at the .01 level and .437 p<.001 at the .05 level for question 2 on the Social Network Satisfaction Scale).

Furthermore, Pearson correlations were run to evaluate the associations between the variables in the preliminary data from this study. There were significant correlations at the .01 level between

measures of support satisfaction in all domains (tangible, emotional informational, and overall) on the Krause Social Support Scale and with scores on the UCLA Loneliness Scale, with correlations ranging between -.342 and -.661, indicating that higher social support is associated with lower loneliness in the preliminary data. Additionally, higher levels of satisfaction with tangible, emotional, and overall social support are significantly associated with lower levels of caregiver burden, as measured by the Zarit Caregiving Scale at the .01 level. Interestingly, higher satisfaction with the informational backing is also significantly associated with lower caregiver burden at the .05 level. The score on the Positive Aspects of Caregiving Scale was associated with the resilience 3 subscales for family cohesion and social resources at the .05 level (.278 $p<.024$ and .288 $p<.019$, respectively). There was an association between satisfaction with tangible support on the Krause Social Support Scale and the social resources and family cohesion subscales of the Friborg Resilience Scale at the .01 level.

In summary, higher social network satisfaction is linked to lower caregiver burden and loneliness, as well as higher social well-being and resilience. The findings suggest that caregivers more satisfied with their social networks experience less caregiver burden and loneliness and report higher overall well-being and resilience. These significant findings indicate that these associations are worth investigating further. It is worthwhile to assess network compositions most likely to support caregiver resilience. Additionally, utilizing qualitative methods and geospatial tracking will be valuable to understanding how support systems function in space and affect caregiver burden and resilience.

We are preparing to conduct data analysis with the full sample - including the specific ego-centric social network data components not discussed above.

**Proposed One-Year and Long-Term Outcomes:**

Our aim in this study is to identify ADRD unpaid caregivers' attributes and understand which social network compositions are most effective in supporting caregiver well-being and resilience. Through this work, we are expanding social network data collection and analysis in dementia research beyond the caregiver-care recipient dyad, recognizing that individuals exist in broader networks. This research has already informed the development of appropriate measures to assess diverse caregivers and interventions that strengthen effective network structures and relationships among caregivers, PLWD, and formal care providers. The research will provide a theoretical understanding of the usefulness of networks in older age.

We will publish a minimum of two peer-reviewed publications from this research. We will present at conferences and lecture series and share with caregivers and PLWD in community settings (e.g., fact sheets). Future Research: Ultimately, the data will inform future research grant applications that will involve collecting longitudinal data examining changes in the social network structure of ADRD caregivers and the development of an intervention targeting effective network compositions that best support ADRD caregivers.

**Year-End Progress Summary:**

Explanation for challenges encountered: The most significant challenge relates to the start date. While we were awarded funds in July 2023, it was in late September that a research account was established. This delayed the hiring and training research assistants, recruitment activities, and data collection. The second most significant challenge was an onslaught of non-eligible participants presenting themselves as eligible participants. This included participants recruited from the ARDC Registry. We determined that non-eligible participants exploited a loophole in our recruitment and eligibility process. They presented themselves as eligible, living in the state and serving as caregivers. They were predominantly from African Nations using VPNS to fake their

locations. We overcame this through additional measures in our scheduling software, including VPN limiting. We also communicated with Banner about these challenges related to the ARDC Registry. Unfortunately, our data review determined that six completed interviews were from these false participants. We have excluded their data from the study and have switched our incentive structure to require physical addresses.

**Progress towards year one outcomes:** As of July 1, 2024, we have completed data collection for 87 of the proposed 100 individuals. We believe we would have achieved all 100 participants without the challenges associated with false participants. Using internal funds, we are attempting to recruit and collect data from the remaining 13 participants before the launch of recruitment for Year 2 (Phase 2) in August 2024. We are also adapting our recruitment strategy for Phase 2 to include greater direct recruitment through service providers.

We have developed infrastructure to support these ongoing research projects and the development of the Social Networks Among Caregivers Research Lab, including the engagement of eleven research assistants (5 3

undergraduate, 1 Master's, and three doctoral students) and eight research practicum students. In doing so, exposing them to ADRD research is a potential career direction.

Additionally, this work has provided valuable insights into the collection of ego-centric social network data over the telephone that has assisted us in refining the data collection strategy for Year 2. We have adopted the lessons from this study to other studies and created a replicable process for managing data collected through these studies.

**Additional highlights of our long-term goals include:**
**Progress on long-term outcomes: Internal Funding**: We secured internal funding from the Edson Dementia Pilot Program for $25,000 to support GEO + SNAC. Through this project, we will pilot the collection of spatial social network data related to their caregiving experience to examine spatial social networks (i.e., activity spaces) and the associated network composition of dementia caregivers over two weeks. External Funding: We have connected with other scholars who shared an interest in this work; we were able to use our experience in the development and submission of external grants. We submitted a proposal to the Department of Defense Congressionally Directed Medical Research Program Peer Reviewed Alzheimer's Research Program Transforming Research Award in June 2024. We plan to submit an R01 to NIA in October 2024, focusing on the longitudinal changes in the social network structure of ADRD caregivers. These grants would extend this work to include greater analysis and data collection opportunities. **Publications and Presentations:** We have one manuscript under review, a study protocol of the work, and a second manuscript in preparation, a systematic review of the literature focusing on research engaging caregivers, their social networks, and their activity spaces. We anticipate that this manuscript will be submitted by July 2024. We are also preparing a manuscript with year-one data to assess time in a caregiving role with network size and resilience. We have also presented the development of this work to the University of Washington Prevention Institute and the Cleveland Clinic Las Vegas E-ADRC Collaborative. We will submit an abstract to present this work at the Arizona Alzheimer’s Consortium 2024 Annual Scientific Conference.

We thank the Arizona Alzheimer’s Disease Research Center for supporting these activities and look forward to ongoing collaboration.

**ARIZONA ALZHEIMER'S CONSORTIUM**
**2023-2024 Scientific Progress Report**

**The Effects of Psilocybin Treatment on Epigenetics and Cognitive Behavior in Typically Aging Mice.** Candace R. Lewis, PhD, Sarah E. Mennenga, PhD, M. Foster Olive, PhD, Jessica Verpeut, PhD. Arizona State University; Arizona Alzheimer's Consortium.

**Specific Aims:**
AIM 1: Determine the effects of psilocybin treatment on learning/memory and anxiety/depression in aged mice.
AIM 2: Determine the effect of psilocybin treatment on DNA methylation in relevant brain regions.

**Background and Significance:**
The broad therapeutic potential of psychedelics indicates that they could be a potential pharmacological treatment for age-related cognitive and behavioral deficits. Psilocybin, a serotonergic psychedelic, is increasingly being recognized for its long-term therapeutic value in treating a variety of neuropsychiatric disorders. Psilocybin is a potent agonist for the 5HT2A receptor (5HT2AR), which is highly expressed in regions of the brain vulnerable to chronic stress such as the prefrontal cortex (PFC) and hippocampus. In humans, psilocybin increases functional connectivity and produces global increases in cerebral glucose metabolism. Across disorders, psilocybin induces therapeutic effects within hours following administration, and lasts well beyond drug elimination, suggesting the induction of neuroplastic mechanisms, which has been verified in animal models. Serotonergic psychedelics reduce inflammation, which may convey improved brain health. Psilocybin treatment rapidly alters expression of 1000's of genes in brain, which may be related to altered epigenetics. This proposal will test the hypothesis that psilocybin alleviates age-related cognitive deficits and depressive- and anxiety- like behaviors in normally aging mice.

**Preliminary Data, Experimental Design and Methods:**
**Animal housing:** 80 aged (20/sex/treatment group, 12-16 months old) C57BL/6J mice (Jackson Laboratories, Bar Harbor, ME, USA) will be kept on 12-h reverse light/dark schedule (lights off at 7 AM) with laboratory chow (PicoLab Rodent Diet 20, #5053; PMI Nutrition International, St. Louis, MO, USA) and water given ad libitum. Age of mice was chosen based on prior research demonstrating that at 16 months physiological function is sufficiently decreased but still has a room for improvement.
**Determination of estrous cyclicity:** Since estrous cyclicity can influence behavior 67, vaginal lavage will be collected from female mice to assess their hormone and estropause status prior to (2 days) and after testing is complete each day. Wet smears will be put immediately onto slides (Superfrost/Plus, Fisher Scientific, Pittsburgh, PA, USA) and visualized under a brightfield microscope to determine estrous cyclicity.
**Psilocybin treatment:** After one week's acclimation, the mice will be randomized into either saline or psilocybin treatment (n = 20/sex/group). Each animal will receive two intraperitoneal injections of either saline (1 ml/kg) or psilocybin (1/mg/kg) one week apart. Dose was selected based on previous psilocybin-induced gene expression and behavior studies.
Proposed One-Year and Long-Term Outcomes:

| Outcome | Year 1 | Year 2 |
|---|---|---|
| Purchase/acclimate cohort 1 | X | |
| Run cohort 1 (n = 20/treatment) | X | |
| Sack/brain harvest cohort 1 | X | |
| Purchase/acclimate cohort 2 | X | |
| Sample receiving cohort 1 | X | |
| DNA isolation quant/quality | X | |
| Methylation arrays | | X |
| Run cohort 2 (n = 20/treatment) | | X |
| Sack/brain harvest cohort 2 | | X |
| Sample receiving cohort 2 DNA isolation quant/quality | | X |
| Methylation arrays | | X |
| DNA methyl data processing | | X |
| Study analyses | | X |
| Manuscript 1 | | X |
| NIMH or NIA R01 | | X |

**Year End Progress Summary:**

During Year 1 of the funding period, the PI and study team will have: secured regulatory approval to conduct the research (including IACUC and US DEA licensure for the controlled substance needed for the project), established a colony and behavior space to accommodate the aims of the project, completed behavior testing and tissue collection for all mice, processed all collected behavior video files, and began isolation of DNA from brain tissue samples. The remainder of the DNA isolation, methylation arrays, and data analysis/manuscript preparation/grant submission is planned for Year 2 of funding.

Our team received IACUC approval to conduct the behavioral component of the proposed research in collaboration with the laboratory of Dr. Jessica Verpeut, an investigator in the Psychology Department at ASU. We also formed a collaboration with Dr. Foster Olive in the ASU Psychology Department to amend his existing schedule I researcher license with the DEA for psilocybin research. Both tasks were completed **during the first quarter of Year 1.**

Dr. Sarah Mennenga, a collaborator on the grant that was formerly located at NYU Langone, relocated to the School of Life Sciences at ASU to coincide with the start of the project. In collaboration with Drs. Olive, Verpeut, and Mennenga, we trained and onboarded a team of behavior testers in the second quarter of Year 1. At the end of Year 1, we have completed behavioral testing for this study (80 aged (20/sex/treatment group)).

Our team has also initiated a collaboration with the laboratory of Dr. Matthew Huentelman at TGen to use their specialized equipment for isolation of DNA from very small (i.e., µgs) low-DNA yield brain samples of medial prefrontal cortex and hippocampus from each mouse. We are currently working on DNA isolation. Once DNA isolation is complete, quantification and quality will be completed, and samples will be processed for methylation arrays. We anticipate completing data collection (i.e., behavior testing scored and methylation array results received) by the end of the second quarter of Year 2 (as proposed).

The final two quarters of Year 2 will be dedicated to data analysis, manuscript preparation, and grant submission planning (as proposed).

In Year 1, Drs. Mennenga, Lewis and Olive submitted two related (unsuccessful) NIH proposals (R01 and R22) to NIDA. The R01 has been revised and resubmitted to NIDA under a new NOSI for epigenetic mechanisms related to addiction. We are awaiting the summary statement for the R22.

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**The Topological Landscape of Proteins Associated with Neurodegenerative Disease.** Eleni Panagiotou, PhD, Kenneth S. Kosik, MD. Arizona State University; University of California, Santa Barbara; Arizona Alzheimer's Consortium.

**Specific Aims:**

(1) The mathematical classification of tauopathies: The goal is to provide meaningful quantitative methods for classifying tauopathies by creating and employing novel mathematical concepts to analyze experimental data of protein structure. The expected outcome is a quantitative description of tauopathies that provides new insight into the relation between sequence, structure and multi-chain organization. This novel analysis will provide the rigorous foundations upon which tauopathies can be identified and studied in experiments and simulations, complementing clinical diagnosis and prognosis.

(2) The topological landscape of tauopathies: The goal is to fully leverage the abundant experimental data deposited in the Protein Data Bank (PDB) and data from Alphafold to create a context that could explain the topological landscape of protein aggregation. The hypothesis is that protein aggregation can be described by a pathway on the mathematical topological landscape of proteins. The expected outcome is a novel framework for understanding protein aggregation, which points to methods of intervention. This approach breaks the barriers of previous studies using novel mathematics from topology and experimental data for understanding protein aggregation.

(3) Topologically selected site mutations: The goal is to leverage the knowledge obtained from Aims 1 and 2 in order to predict site specific mutations that quantitatively alter a protein's topological landscape in a way that can be experimentally tested. The expected outcome is the proof of concept that the topological landscape of proteins can be altered experimentally. In the long term, this could lead to the development of methods of prediction of disruption of protein aggregation and lead to the creation of novel site specific, innovative therapeutics.

**Background and Significance:**

Background: Structure and function are inextricably linked properties of proteins. At the center of many neurodegenerative diseases is the misfolding and aggregation of specific proteins into abnormal conformations that are associated with toxicity. Despite a lot of scientific advances in understanding the connection between sequence and structure over the past 40-50 years, aspects of protein folding, misfolding, and multi-chain organization of proteins, still remain elusive. To some extent, this is because there are currently no methods that can accurately quantify each amino-acid position's contribution to local and global inter- and intra-chain topology and geometry of proteins. Significance: Understanding the topological characteristics associated with energetic wells would enable to create topological barriers to it. Establishing structure-activity relationships (SAR) among these different states, a prerequisite for proper drug targeting, is exceedingly difficult. A screening method to choose sites and co-factors for disrupting protein aggregation is needed. Putting a rigorous framework for disrupting tau protein aggregation will enable the generalization to other proteins as well.

**Preliminary Data, Experimental Design and Methods:**

The simplest measure of topological complexity of open or closed curves in 3-space is the Gauss linking integral. It measures the degree of linking between two curves. It can be applied over one curve, called Writhe, to measure its degree of interwinding, but it cannot detect knotting accurately, as it is influenced by local geometry. The second Vassiliev measure (introduced by the PI, as an extension of the second Vassiliev invariant) can instead measure knotting

complexity. For multi-chain systems, of open or closed curves, the Jones polynomial can be used to measure their collective topological complexity (via a method introduced by the PI). These tools are ideally predisposed to enable the creation of a rigorous topological model of protein folding/misfolding upon which transient in time conformations can be analyzed locally or globally that can be associated with protein dynamics, function and evolution. Preliminary results have shown that these topological metrics of structural complexity of the native state of proteins correlates with their experimental folding rate. Moreover, novel methods introduced by the PI have the potential to predict specific sites where mutations may alter the global conformation of a protein.

**Proposed One-Year and Long-Term Outcomes:**

We will develop novel mathematical methods that enable the quantification of local and global topological differences of different tauopathies based on topological metrics, which we will apply to experimental structures deposited in the PDB. First, we will analyze the topology of single filaments associated to different tauopathies and our results will become available in manuscripts and, in the long term, an online database. We will create a pairwise linking matrix fingerprint to analyze the linking and relative position of protein fragments in different tauopathies. We will use experimental data and molecular simulations in combination with topological analysis to identify the local and global topological energetic wells and how local mutations or other cofactors enable the proteins to overcome energetic barriers that lead to misfolding. We will use our theoretical analyses to propose sites where mutations or binding may alter the topological landscape of proteins, which, in the long term, we will test experimentally.

**Year End Progress Summary:**

Neurodegenerative diseases, like Alzheimer's, are associated with the presence of neurofibrillary lesions formed by tau protein filaments in the cerebral cortex. While it is known that different morphologies of tau filaments characterize different neurodegenerative diseases, there are few metrics of global and local structure complexity that enable to quantify their structural diversity rigorously. We employed for the first time mathematical topology and geometry (in particular, the Gauss linking integral, writhe and second Vassiliev measure) to classify neurodegenerative diseases by using cryo-electron microscopy structures of tau filaments that are available in the Protein Data Bank (PDB). This enabled to achieve a consistent, but more refined classification of tauopathies, than what was previously observed through visual inspection. Our results reveal a hierarchy of classification from global to local topology and geometry characteristics. In particular, we find that tauopathies can be classified with respect to the handedness of their global conformations and the handedness of the relative orientations of their repeats. Progressive supranuclear palsy (PSP) is identified as an outlier, with a more complex structure than the rest, reflected by a small, but observable knotoid structure (a diagrammatic structure representing non-trivial global topology). This topological characteristic can be attributed to a pattern in the beginning of the R3 repeat that is present in all tauopathies but at different extent. Moreover, by comparing single filament to paired filament structures within tauopathies we find a consistent change in the side-chain orientations with respect to the alpha carbon atoms at the area of interaction.

Recent studies of misfolding and aggregation of tau proteins point to specific sites or motifs of interest along the protein. Our results show that mathematical topology/geometry of cryo-EM structures alone identifies the PGGG motifs and the PHF6 and PHF6* motifs as sites of interest, which are known to regulate the aggregation capacity of tau protein experimentally. In addition, our results show a geometrical hierarchy of the PGGG motifs that differs for the 3R, 3R+4R and 4R tauopathies. We also employed the local topological free energy (LTE), a method of characterizing the topology of tau filaments relative to the topology of the folded state ensemble

of proteins in the PDB by analyzing a culled data set of more than 13K proteins. Our results showed that progressive supranuclear palsy (PSP) is the only tauopathy (along with the similar GGT) with a high LTE conformation at residues 302 - 305, which is in the vicinity of the 301 site, where mutations have shown experimentally to promote aggregation. These residues are also contained within the region of the jR2R3 peptide which is known experimentally to form fibrils that adopt a fold characteristic of 4R tauopathy fibrils and in particular PSP and GGT. We extend our mathematical method to define the topological energy at multiple length and study the topological energy of the jR2R3 motif and of the repeats. We find that the jR2R3 motif of 4R tauopathies (and in particular PSP and GGT) has the lowest topological energy, implying that it is more stable, in agreement with experiments. By comparing R2 repeats of misfolded tau proteins with tau protein bound to microtubules and filamentous actin, we find that structures of misfolded tau R2 repeats are locally more stable and points to binding being associated with higher LTE values. The topological energy of the entire R2 repeat however is lower for bound structures, suggesting that high LTE local conformations may stabilize the global structure of a protein. We analyze the LTE of all known tau protein antibodies that are known to bind to tau filaments. Our results demonstrate that binding occurs with higher probability at the high LTE sites of an antibody. This may point to a method of predicting sites of binding for possible tau antibodies that could be used as a screening method for antibody selection.

Finally, by employing coarse grained molecular dynamics simulations of full-length tau proteins in solution, we find that co-factors such as RNA and stress can affect the topological landscape of tau proteins. In particular, we find that they reduce the total local topological free energy of tau. The data also shows that knotting of a tau protein in the unfolded ensemble is a possible but rare event.

Challenges were encountered in recruiting graduate students. These were addressed by broad efforts of the PI to engage more students in the research and led to hiring multiple graduate students.

The following paper was published:

1. Sugiyama, M., Kosik, K. S. and Panagiotou, E., 2024, Mathematical topology and geometry-based classification of tauopathies, Scientific Reports, 14, 7560

The following papers are in preparation:

2. Sugiyama, M., Kosik, K. S. and Panagiotou, E., 2024, Geometry-based prediction of tau protein sites associated with misfolding and aggregation , in preparation
3. Sugiyama, M., Najafi, S., Kosik, K. S. and Panagiotou, E., 2024, The coarse-grained topological landscape of disordered tau proteins, in preparation

The PI participated in the 2024 AAC Annual Scientific Conference and the 2024 AAC Retreat where she had the opportunity to present the new results (with a poster and talk, respectively) and interact with other scientists and seek new collaborators. The PI also visited collaborator Dr. Ken S. Kosik in order to advance this research.

The PI applied and was awarded the following funding support for continuation of this research: July 2024 – June 2025 ASU Women in Philanthropy, Mathematics against Alzheimer’s disease, $49,096.

The results of this research show that mathematical topology and geometry provides insights into protein misfolding and aggregation, as well as predicts sites of interest in proteins related to binding and conformational stability that could be used for selection of site-specific tau antibodies. These results will be the basis for seeking further support from institutions such as NIH and/or NIA for computational and lab experiments that can verify our hypotheses.

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Dementia and Mild Cognitive Impairment in Adults Experiencing Homelessness.** Heather M. Ross, PhD, DNP, Diana M. Bowman, PhD, CASS (Central Arizona Shelter Services); St. Vincent de Paul. Arizona State University; Arizona Alzheimer's Consortium.

**Specific Aims:**

1) Implement dementia and mild cognitive impairment (MCI) screening in the shelter intake process for older adults experiencing homelessness in the Greater Phoenix Region.
2) Describe the prevalence of dementia and MCI in people experiencing homelessness who are seeking shelter services in the Greater Phoenix region.
3) Encourage participation in the City of Phoenix voluntary dementia registry program for shelter clients who screen positive for dementia or MCI.

**Background and Significance:**

Older adults represent the fastest growing segment of the population in Phoenix, Arizona, leading Phoenix to have one of the fastest growing populations of people with dementia and mild cognitive impairment (MCI) (Ross et al., 2022). Older adults also represent the fastest growing segment of the homeless population in Phoenix. From 2007-2017, there was a 50% increase in older adults as a percentage of people experiencing homelessness (Joint Center for Housing Statistics, 2019); this number is expected to triple by 2030.

First responders in Phoenix report that they routinely respond to calls for service from older adults, both housed and unhoused, who appear to be confused. Indeed, dementia is frequently noted to be a contributing factor to homelessness in older adults (Piña-Escuerdo et al., 2021). However, first responders report a significant gap in identifying individuals with dementia or MCI, particularly those individuals who are experiencing homelessness and may lack meaningful access to primary care or advanced neurology services. As a result, first responders are limited in their ability to effectively connect individuals with supportive services, which often leads to a revolving door phenomenon of homelessness, poor health outcomes, diminished life expectancy, and additional cognitive barriers preventing individuals from effectively accessing services (Piña-Escuerdo et al., 2021). There is limited research evidence characterizing the prevalence of dementia for people experiencing homelessness and an identified need for studies to better enumerate the prevalence and intersectional experience of dementia in people experiencing homelessness beyond the veteran population (Babulal et al., 2022).

**Preliminary Data, Experimental Design and Methods:**

As of 2023, there were no dementia screening programs established in Phoenix-area homeless services agencies and no data describing the prevalence of dementia in people experiencing homelessness in Phoenix, Arizona.

**Proposed One-Year and Long-Term Outcomes:**

- One-Year
  - 100% of CASS staff will be trained to implement MoCA screening tool.
  - MoCA screening tool will be adopted into standard intake protocol for CASS clients age 55+.
  - Protocol for clients to register in City of Phoenix voluntary dementia registry will be established.
  - 80% of clients will be screened with MoCA on intake to CASS Haven shelter.
  - Preliminary data on dementia, MCI prevalence in older adults experiencing homelessness in Phoenix.

- Prevalence data for dementia and MCI in older adults seeking non-veteran emergency shelter services for homelessness will be described, addressing a significant gap in the dementia literature.
- Grant submissions for further funding of expanded implementation of MoCA screening across sites providing services to older adults experiencing homelessness (e.g., PCORI, NIH).

• Long-Term
- Increased community uptake of voluntary dementia registry.
- Older adults with dementia/MCI experiencing homelessness in Phoenix will receive appropriate therapy and supportive care for dementia/MCI.
- Reduced incidence of homelessness for people with dementia/MCI.
- Public safety encounters for people with dementia/MCI will result in connection to appropriate dementia/MCI services.
- Fewer repeat shelter stays for people with dementia/MCI.
- Integration of dementia/MCI screening with future comprehensive SDoH, mood disorder screening for improved comprehensive care of older adults at risk and experiencing homelessness.
- Longitudinal prevalence data for dementia and MCI in older adults seeking non- veteran emergency shelter services for homelessness will be described, addressing a gap in the dementia literature.

**Year End Progress Summary:**

One-Year Outcomes:

As of June 30, 5 of 6 proposed one-year outcomes were met. 100% of CASS case management staff have been trained to perform MoCA screenings including paper-pencil and tablet-based screenings. (Outcome Met) The MoCA screening tool has been adopted as a standard component of senior intake evaluations for CASS clients aged 55+. (Outcome Met) More than 80% of clients entering the CASS Haven site in October-November 2023 were screened with the MoCA tool. (Outcome Met) We published findings in Alzheimer's & Dementia from the first 112 clients screened, including prevalence of positive screenings for the population. (Outcome Met) We submitted four grants to Vitalyst Foundation (successful), Department of Justice (pending), and National Institutes of Health (1 pending, 1 declined) to expand the work including establishing dementia screening at additional shelter and non-shelter sites, establishing dedicated pathways for dementia diagnosis for emergency shelter clients, and creating culturally- relevant feedback forms for MoCA screenings in non-clinic settings. (Outcome Met) Additional grant proposals to NIH are in preparation.

We were not able to meet the proposed outcome of establishing a protocol for clients to register in the City of Phoenix voluntary dementia registry as the registry requires a stable address for registration that is not possible for people experiencing homelessness. We are continuing to work with the Phoenix Police Department to identify a strategy to overcome this challenge.

Long-Term Outcomes:

As of June 30, we have made definitive progress toward 1 of 5 long-term outcomes, and incremental progress toward 4 of 5 long-term outcomes.

In partnership with CASS and Circle the City, we submitted a successful grant to Vitalyst Foundation to establish a dedicated pathway to dementia diagnosis and care for CASS clients with a positive MoCA screen. The dedicated dementia diagnosis clinic visits will begin on August 1, 2024. (Definitive Progress to Outcome)

As described with our one-year outcome regarding the City of Phoenix dementia registry, we are working with the Phoenix Police Department to overcome an unforeseen barrier around

permanent address requirement for the registry. Our conversations are positive, but significant modifications to departmental protocols will be needed to overcome the address barrier. Therefore, we continue conversations toward an eventual solution. In addition, we recently submitted a grant in partnership with the Phoenix Police Department to incorporate MoCA screening into their practice for Crisis Intervention Team officers. We anticipate that with increased community screening by the police department, we will see increased community uptake of registry services. (Incremental Progress to Outcome)

We are currently preparing a proposal to expand shelter intake screenings for older adults to include comprehensive screenings for social determinants of health risks to inform coordinated support services for older adults when transitioning from shelter to stable housing. We hope that this screening program will result in improved outcomes for older adults exiting homelessness, and will motivate further upstream screening for vulnerable adults as a measure to prevent future homelessness. (Incremental Progress to Outcome)

We continue to collect screening data, including repeated screenings for shelter clients on transition between congregate and non-congregate settings, providing longitudinal prevalence data. We will continue to collect these data in partnership with community agencies, and look forward to being able to report on longitudinal prevalence in the context of shifting conditions for unhoused adults over time. (Incremental Progress to Outcome)

Our long-term outcome goal of reduced incidence of homelessness for people with dementia/MCI will require significant interim progress. However, we have two pending grant proposals that, if funded, will allow us to increase appropriate connection to services for public safety encounters and reduce repeat shelter stays by helping to keep older adults stably housed after exiting homelessness. (Incremental Progress to Outcome)

# ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Comparing Older Adult Stress Levels Associated with Cognitive and Motor Testing to Advance Earlier Dementia Screening.** Sydney Schaefer, PhD, Michael Malek-Ahmadi, PStat, PhD. Arizona State University; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

**Specific Aims:** The specific aim of this project is to compare test-related stress levels between cognitive and motor tests in older adults.

**Background and Significance:**
Alzheimer's disease is the most common type of dementia, affecting 1 out of every 9 older adults in the US. However, primary care providers (PCPs) miss almost half of all cases, even though nearly all older adults see their PCP on an annual basis. Despite regular interaction with their PCP, only 16% of older adults receive routine cognitive testing to screen for early signs of AD or other dementias. This is surprising, given that 4 out of 5 older adults say they would want to know if they had AD in early stages. The primary reasons why PCPs choose not to assess cognition are 1) an apparent lack of symptoms or complaints from a patient, 2) the lack of time during a patient visit; and 3) and patient resistance to being tested. One plausible mechanism behind patient resistance is that older adults may experience stress and anxiety in response to cognitive testing, particularly in those who are already experiencing cognitive decline. Thus, there is a clear need for an objective, brief, and patient-friendly screening tool in primary care to guide PCPs in referring patients for further diagnostic neuropsychological evaluation.

To address this clinical need, we have developed an objective performance-based test and tested it in >500 cognitively unimpaired older adults and those with Mild Cognitive Impairment or probable AD. Our test is simple and short enough for it to be feasibly administered in primary care by nursing staff along with other vitals (e.g., pulse, blood pressure) prior to the PCP time with the patient. Our clinical research has shown that our test correlates with disease status, predicts the extent of AD progression over one year, and is associated with AD biomarkers like brain amyloid and cortical atrophy, particularly of the hippocampus. Our test can also differentiate between AD and Parkinson's disease, indicating that test performance is resistant to motor symptoms like tremor and bradykinesia. Because it is procedural rather than semantic or declarative in nature, we hypothesize that our test will induce less test-related stress than a cognitive screen, which will improve patients' willingness to be tested.
To measure test-related stress, we collected electrodermal activity (EDA) during testing as well as subjective reports of state-based stress in response to completing either the cognitive test or the performance-based test.

**Preliminary Data, Experimental Design and Methods:**
This project was based on preliminary data from a prior study that measured electrodermal activity (EDA) using commercial wearable sensors during cognitive testing in younger adults, finding that the delayed recall portion was associated with the highest level of EDA (relative to immediate recall, orientation, and concentration). This provided strong proof-of-concept that EDA will be sensitive to stress (or a related emotional state) during cognitive testing in older adults, as tested here.

In this study, we are recruiting 60 cognitively-intact older adults (65 years or older, 50% females) from the greater Phoenix area. To date, we have collected 15 participants, due in part to a delay in securing the necessary lab space for this project in the Arizona Biomedical Collaborative (ABC) building in downtown Phoenix. Participants will be excluded if they have a history of major stroke, head injury with loss of consciousness of >30 minutes, or other diagnoses that may affect cognition; current or past major psychiatric illness (e.g., schizophrenia); history of

substance abuse; current use of antipsychotics or anticonvulsant medications; inadequate manual dexterity; or a Katz ADL Survey score >10.

Electrodermal activity (EDA): EDA is a well established physiologic measure that reflects changes in arousal as changes in the skin's electrical conductance, which is controlled by the sympathetic branch of the autonomic nervous system through sweat secretion. For example, increased sympathetic drive due to high stress, cognitive load, or strong emotional responses results in more sweat secretion than low-activation states (i.e., boredom, low cognitive load), producing higher or lower levels, respectively, of EDA. Furthermore, EDA signals contain a tonic component, a measure of system state or responses over time (measured in minutes or longer) or both, and a phasic component, which offers insight into systemic responses to particular stimuli on the order of milliseconds to seconds. Thus, EDA (particularly the phasic component) has been used as a proxy for quantifying stress and strong emotional responses under numerous laboratory and real- world conditions.

A wireless, wrist-worn sensor (Shimmer3 GSR+) recorded EDA from the dominant hand, sampling at a rate of 16 Hz. These commercially available sensors pass a low electrical current (up to 1100 mAh) between 2 small electrodes (1-cm2 surface area). The units of EDA are microSiemens (μS), which indicate the amount of electrical conductance. Traditionally, EDA is recorded at the fingertip because of the density of sweat glands there that are sensitive to autonomic responses.

Before baseline data collection, participants performed a 2-minute walk at a self-selected pace to generate sweat on the wrists for initializing the sensor, per the manufacturer's recommendation. The sensor was placed on the anterior surface of the right wrist, and participants sat quietly in front of a laptop displaying a blue circle on a white background. Participants were instructed to “clear their minds as completely as possible” during the baseline period to limit any cognitive or emotional activity that could trigger electrodermal responses. The baseline period lasted 5 minutes, which is sufficient for establishing skin-to-electrode contact as evidenced by a stable electrodermal response (indicating a stable autonomic state) and skin temperature (< 0.01 μS and <1°C change over the final 30 seconds). Following baseline, participants were informed that they would be completing either a ‘cognitive test’ (the Montreal Cognitive Assessment) or a ‘motor test’ (the performance-based test). Each participant's entire raw data signal was filtered and smoothed with a moving average window (window length = 16 samples). Data was standardized per wrist following standard procedures to enable interindividual comparisons of electrodermal responses. Data were separated into tonic and phasic components via continuous deconvolution analysis; only the phasic components were analyzed here, where higher phasic activity indicated more stress. We also administered the 6-item short-form state scale of the Spielberger State-Trait Anxiety Inventory (STAI), which has been shown to be sensitive to temporary reactions to adverse events. This was administered at baseline, immediately after participants were told which test they would complete, immediately following test completion, and 30 minutes after test completion. Even though EDA was monitored continuously throughout the study, phasic EDA was extracted from the same epochs as the STAI, and for the purposes of this study, only the change in peak phasic EDA was considered from baseline to immediately after participants were told which test they would complete (i.e., ‘test awareness’). We expect that this captures people’s anxiety (if any) about taking the test itself, and not any test-related anxiety that may arise during the test due to actual task difficulty.

Cognitive testing group: Participants (n=30) completed the Montreal Cognitive Assessment (MoCA). The MoCA is brief yet covers multiple cognitive domains. Its administration time roughly matches that of the performance-based test (see below), enabling us to control for test length between groups.

Performance-based testing group: Participants (n=30) completed our novel test, which we have named the quick Behavioral Exam to Advance Neuropsychological Screening), since it is designed to inform primary care providers whether additional neuropsychological evaluation is needed. This test requires patients to move two raw kidney beans at a time with a plastic spoon from a central home cup to one of three target cups using their nondominant hand in a simple sequence involving 15 movements, equaling one trial. Patients completed six trials in a row, and each trial is timed. A final score is derived from these six trials, where higher values are associated with dementia.

Statistical analyses and Expected results: To test for significant group differences in phasic EDA in response to the type of test administered, we compared the change in phasic EDA from baseline to test awareness between groups using a one-tailed independent t-test.

**Proposed One-Year and Long-Term Outcomes:**

We plan to submit 1-2 manuscripts and present one abstract at the Alzheimer's Association International Conference during the one-year award period. We also plan to submit a Phase I SBIR to NIA (RFA-MD-23-003) to establish feasibility of the qBEANS as an at-home screening tool among underrepresented minorities. Our longer term goal is to develop a patient-friendly method for annual screening of preclinical AD that older adults actually are willing to do, which will translate to earlier disease detection and in turn enable older adults to pursue available treatment, enroll in clinical trials, and/or make appropriate legal/financial plans accordingly.

**Year End Progress Summary:**

To date, we have completed 15 participants across the Cognitive testing group (n=7; 4 females; mean±SD age: 73.1±5.8 years) and the Performance-based testing group (n=8; 5 females; mean±SD age: 75.1±4.3 years). Preliminary results indicated little to no change in the state-based scores on the STAI relative to baseline, regardless of which test they completed ($p=0.72$), suggesting that neither test produced significant levels of self-reported stress. When looking at the EDA data, the cognitive testing group tended to experience a larger increase in peak phasic EDA from baseline to test awareness (mean [95%CI] increase = 0.66 [-0.92, 2.25]) than the performance-based testing group (0.28 [-0.64, 1.21]), although these preliminary results are not significant at this time ($t(1)= 0.53$; $p = .30$). It is unclear at this time whether older adults may find the act of taking a cognitive test more stressful than a novel performance-based test, and we will continue to collect our anticipated sample size of 30 per group to further test our hypothesis.

This study is still ongoing, and we are using discretionary funding and related funds from an awarded Edson New Idea grant (PI: Schaefer) that is investigating saliva-based stress markers associated with completing either a cognitive test or our performance-based test. A major challenge that delayed the start date of our data collection was finalizing new lab space in the Arizona Biomedical Collaborative (ABC) building, which was not approved by ASU KE until February of 2024. We were not able to get sufficient data in time to submit an abstract to AAIC, but will submit a late-breaking abstract of our preliminary results to the 2024 Gerontological Society of America (GSA) Annual meeting. We are also still planning to submit a Phase I SBIR to NIA in response to RFA-MD-23-003 for the December 5, 2024 cycle, and will use data from this project as preliminary data. No publications have emerged from this research yet, but new collaborations with Dr. Shireen Sindi at the Karolinska Institute in Stockholm have arisen from this research. We will meet with Dr. Sindi at AAIC in Philadelphia this year to further discuss our emerging data.

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**The Power of Senses: A Pilot Study on Multi-Sensory Environments and Their Effects on Sleep, Mood, and Stress in Older Adults with Behavioral and Psychological Symptoms of Dementia.** Nina Sharp, PhD, Aaron Guest, PhD, Dongwoo (Jason) Yeom, PhD, Melita Begrave, PhD. Arizona State University; Arizona Alzheimer's Consortium.

**Specific Aims:**

1) Specific Aim 1: Evaluate the effects of exposure to an affordable Multi-Sensory Stimulation Environment (MSSE) in the morning on stress, depression, and agitation in patients with behavioral and psychological symptoms of dementia (BPSD).
2) Specific Aim 2: Assess the impact of exposure to an affordable Multi-Sensory Relaxation Environment (MSRE) in the evening on stress and sleep quality in patients with BPSD.
3) Specific Aim 3: Explore the combined impact of exposure to an MSSE condition during the daytime and MSRE condition during the nighttime on stress, mood, and sleep quality in patients with BPSD.

**Background and Significance:**

The increasing number of older adults diagnosed with dementia, predicted to triple by 2050, presents a significant challenge for caregivers. Caregivers often experience a heavy burden and stress due to the wide range of challenging behavioral and psychological symptoms that those living with dementia may exhibit. Furthermore, BPSD can negatively impact the quality of life and overall well-being of individuals with dementia making it essential to identify effective interventions to manage these symptoms and improve the lives of both patients and caregivers. The MSE is a non-pharmacological intervention that aims to create sensory balance by using controlled visual, auditory, tactile, and olfactory stimuli to reduce overactive or underactive behaviors in individuals with BPSD. Previous research revealed the separate therapeutic benefits of specific lighting, aromas, and sounds in managing BPSD. Daily exposure to proper aroma, lighting, and music has been found to decrease agitated behaviors and enhance cognitive performance, alertness, mood, and sleep quality in patients with dementia. While multisensory environments (MSEs) have generated interest among caregivers as a potential solution for managing BPSD, there is a lack of evidence regarding the specifics of MSE rooms and the timing and duration of exposure. Additionally, no studies have been conducted to compare the effects of a stimulating MSE with those of a relaxing MSE on BPSD symptoms. The cost has also been cited as a frequently encountered barrier to implementing MSEs.

**Preliminary Data:**

Our current and previous studies have assessed sleep, circadian activity rhythms, mood, and cognitive performance in older adults over thousands of hours. Based on our preliminary data, we have found that exposure to a stimulating lighting condition at the appropriate time positively impacts sleep quality, mood, and cognitive performance in older adults. After examining the application of lighting interventions with varying intensity and color in the residential units of healthy older adults, we discovered a significant improvement in objective sleep metrics. We also found a significant reduction in depression scores. In addition, we have previously studied the use of music therapy to elicit improved cognitive skills such as retrieval of newly learned information, attention, and alert responses in various populations, including older adults with and without dementia. Our initial data support music's effectiveness in promoting wellness and cognitive health. While our current and previous studies provide evidence of the usefulness of lighting and music in improving older adults' health and quality of life, it is important to examine the collective

benefits of integrating these elements in addition to aromatherapy in a multi-sensory environment to promote stimulation and relaxation in patients with BPSD.

**Experimental Design and Methods:**

The study was conducted as a within-subject design, with participants undergoing 7 days in a conventional environment (baseline), followed by three 6-day periods of multisensory interventions, each separated by a 7-day washout period. Sleep, stress, depression, and agitation were monitored in each condition. The multisensory interventions were implemented in the common areas of selected behavioral care facilities where older adults with BPSD spend most of their waking hours under the supervision of facility caregivers. (Baseline): Once participants were screened and consented, the baseline measurement was performed to monitor patterns of sleep, stress, depression, and agitation for 5 days under the conventional condition in the facility. Participants were asked to continuously wear a FitBit Sense 2 on their non-dominant wrist for 6 days to track sleep/wake and circadian activity patterns. FitBit Sense 2 is a validated, low burden technique for estimating the timing of sleep and wakes. FitBit Sense 2 were also used to monitor their heart rate variability (HRV) during the waking hours. To assess depression and agitation in participants, two questionnaires, Cornell Scale for Depression in Dementia (CSDD) and Cohen-Mansfield Agitation Inventory (CMAI), were completed by the primary caregivers at the last day of the baseline period. Intervention: The intervention period commenced immediately after the baseline assessment. Our study examined the effects of exposure to three different conditions: (1) a Multi-Sensory Stimulation Environment (MSSE), (2) a Multi-Sensory Relaxation Environment (MSRE), and (3) a combination of the two. Each intervention period last 6 days, with a 7-day washout period. The MSSE and MSRE conditions were purposefully designed to provide a sensory equilibrium through controlled visual, auditory, and olfactory stimuli. These conditions were applied by research personnel in a common area of a selected facility through simple and affordable devices readily available in the market, such as bubble tubes, color-changing floor lamps, ultrasonic aroma water diffusers, stereo systems with speakers. The intervention began with 6 days of exposure to the MSSE environment for four hours every morning. The MSSE condition was designed to create a stimulating environment using therapeutic light, music, and aroma, each selected to incite excitement, alertness, engagement, and cognitive functioning. The MSSE included soft yellow orange indirect lighting, a citrus scent to activate cognitive skills, and fast tempo music with sound of birds. Following a 7-day washout period, participants were exposed to the MSRE condition for three hours every evening for 6 days. The MSRE condition, in contrast to MSSE, was designed to create a relaxing environment to improve comfort, rest, and reduce stress through purple color lighting, quiet music with a slow tempo, and a lavender scent. The third intervention period entailed exposing participants to both the MSSE and MSRE conditions, once in the morning and once in the evening, to investigate the combined benefits of the two interventions on sleep, stress, depression, and agitation in patients with BPSD.

**Proposed One-Year and Long-Term Outcomes:**

Successful study completion provides empirical evidence for multi-sensory interventions like MSSE and MSRE in improving the well-being of older adults with BPSD. The findings contributes to the growing literature on non-pharmacological interventions, potentially reducing reliance on harmful medications and improving overall care quality. The study's initial results will be presented at the 2024 GSA Annual Meeting and EDRA 55, and the results will be published in prestigious journals such as the Journal of Aging and Environment, and Environmental Psychology. Further dissemination will occur among long-term care service providers and community partners. Additionally, the outcomes of this project will serve as preliminary data for follow-up proposals for external funding (i.e., NIA). Finally, the project may lead to increased awareness and adaptation of non-pharmacological interventions for older adults with dementia, reducing reliance on potentially harmful medications and improving the overall quality of care.

**Year End Progress Summary:**

Because this type of population is vulnerable and resides in special facilities that maintain high standards of privacy as well as the involvement of caregivers, the IRB process took quite a long time before it was processed. We contacted the manager of the memory care facility "Sunshine Village," where we conducted a previous study, and he nominated another memory care facility, "Fairmont Village." The study took place in a behavioral unit. Fifteen candidates were contacted, and only twelve agreed to participate. Of the twelve, eleven participants completed the study protocol, and one was excluded due to noncompliance with the study protocol.

The multisensory environment equipment was installed in the common area of the facility. We started week 1 as a training week for the caregivers on how to fill out the surveys and how to monitor the Fitbit. Furthermore, during the training week, we tested the multisensory stimulating environment as well as the multisensory relaxing environment to adjust these environments based on the participants' comfort and to ensure no negative reactions would be caused by these interventions.

In week 2, which is considered week 1 of data collection, we started the actual study and began collecting data for the baseline condition. For each intervention, we considered five days of data collection (Monday-Friday). Sleep and heart rate were recorded daily. The CMAI and CSDD surveys were printed and delivered to the caregivers (morning shift and evening shift) on the last day of each intervention week. In week 3, we started the multisensory stimulating environment, which ran from 6:00 AM to 10:00 AM. The following week (Week 4) was a washout period, and no data was collected. In week 5, we started the multisensory relaxing environment, which ran from 5:00 PM to 8:00 PM. The following week (Week 6) was another washout period, and no data was collected. In week 7, we began the combination intervention, with two interventions per day: the multisensory stimulating environment from 6:00 AM to 10:00 AM and the multisensory relaxing environment from 5:00 PM to 8:00 PM.

The research assistant went to the memory care facilities daily during the intervention times to start/end the interventions (switching on/off the equipment, including the lights, aroma, and music) and to observe/monitor the interventions to ensure that the participants were exposed for at least 30 minutes to each intervention. At the end of each intervention week, the research assistant scheduled meetings with the caregivers and interviewed them to fill out the CMAI and CSDD surveys. In week 8, the research assistant went to the facility to pick up the research equipment.

During the interventions, we received the following comments from the caregivers: some patients who used to wander exhibited less wandering under the intervention as they tended to remain seated. We finished data collection and are currently analyzing the data. Preliminary data analysis showed that the interventions significantly lowered depressive symptoms compared to the baseline. However, the intervention conditions were observed to increase agitation (except for physical aggression) compared to the baseline. No significant improvements were observed in sleep quality.

Initially, heart rate variability (HRV) was one of the variables intended to predict participants' stress levels during intervention periods. However, despite daily recordings of participants' heart rates, there was a lack of HRV measurements, potentially due to the limitations of the Fitbit Sense 2 in measuring HRV within this population. Consequently, heart rate was used as an alternative to predict stress among the participants. Observations indicated that participants' heart rates were lower during intervention times compared to the baseline condition. These initial findings were presented at the Environmental Design Research Association (EDRA) 2024 conference in Portland, OR. In addition to analyzing the current study's data, we are preparing a follow-up study to investigate the impact of one Multi-Sensory Environment (MSE) variable, Aroma.

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Intracellular Targeting of Toxic Tau Variants as a novel treatment for Alzheimer's Disease.**
Michael Sierks, PhD. Arizona State University; Arizona Alzheimer's Consortium.

**Specific Aims:**
Our objective is to demonstrate that selectively targeting toxic tau variants in an hiPSC cell line expressing R306W tau provides significant therapeutic benefit. To achieve this objective, we have devised the following specific aims:
**Aim 1.** Express tau variant targeting nanobodies in a neuronal cell culture expressing an AD related mutant tau variant. We identified six nanobodies that selectively bind human AD based tau variants and block neuronal toxicity of the targeted variants [1]. Here we will separately insert each of the six nanobody genes into a mammalian cell expression vector. We will culture the R306W tau hiPSC cell line to generate a neuronal phenotype and then transform the cells with the mammalian cell expression vector. The nanobodies will contain a peptide tag to facilitate transport in and out of neurons enabling the nanobodies to bind and remove the target tau variant from cells as previously demonstrated [2].
**Aim 2.** Assess therapeutic potential of each nanobody using an in vitro screen with the R306W hiPSC cell line. Each of the nanobodies will be separately expressed in the hiPSC cell line by transfection with the mammalian expression vector. A vector expressing GFP will be used as a control. The goal is to identify the two most promising anti-tau therapeutics for further testing in an in vivo AD tau mouse model

**Background and Significance:**
Pathologically, AD is characterized by the presence of neuritic plaques and neurofibrillary tangles in the brain. The principal component of the extracellular neuritic plaques is the β-amyloid protein (Aβ), while the neurofibrillary tangles are composed of tau, a phosphorylated microtubule-associated protein. Substantial evidence indicates that pretangle oligomeric tau species rather than fibrillar forms are responsible for the neurodegenerative phenotype. The scientific premise of this proposal, based on extensive literature, is that specific AD associated conformational variants of tau play key toxic roles in early stages of AD and they represent promising therapeutic targets for treating AD providing they can be effectively targeted. Because of the importance of tau in neuronal function, for safe long-term therapeutic applications, it is critically important to selectively target only toxic tau variants.

**Preliminary Data, Experimental Design and Methods:**
Preliminary Data. Since tau is found in a variety of different conformationally distinct forms in the human AD brain, reagents are needed that can selectively bind key AD related variants of these neuronal proteins. We developed a panel of antibody-based (nanobody) reagents that selectively bind disease related protein variants of key neuronal proteins including tau, Aß, alpha- synuclein and TDP-43. We showed that the presence of specific oligomeric tau and Aß variants in human blood samples are promising biomarkers for AD, and that the nanobodies can be used to readily identify blood samples of presymptomatic AD cases We demonstrated that nanobodies can selectively target and clear toxic protein variants in both cell and animal models of neurodegenerative disease.

Experimental Designs and Methods. Aim 1. Generate mammalian expression vectors. We will generate mammalian expression vectors expressing the six anti-tau nanobodies as well as a control vector expressing GFP. Each construct will contain an N-terminal secretory signal to

secrete the protein from infected cells and an N-terminal tag to promote transfer into and out of neurons.
Aim 2. In vitro screen of tau nanobodies. We previously generated a pool of nanobodies that selectively bind tau variants present in human post-mortem AD brain tissue but not age matched cognitively normal controls. We identified 6 nanobodies that inhibit neurotoxicity induced by addition of exogenous tau preparations isolated from human post-mortem AD brain tissue. For the in vitro screen of these six nanobodies, we will utilize an hiPSC line expressing the R306W tau mutation. We will then assess neuronal health by presence of aggregated tau protein, increase in lethality, and change in MTT and LDH levels as described previously.

**Proposed One-Year and Long-Term Outcomes:**
Here we propose to test a novel therapeutic approach for treating AD. We have generated a panel of nanobody reagents that selectively bind tau variants that are uniquely present in human AD brain but not age matched cognitively normal brain tissue. From this panel of nanobodies, we identified six different nanobodies that can neutralize toxicity of exogenously added tau preparations from human AD brain. We have also shown that these nanobodies all recognize tau variants generated in mouse models of AD. Since tau is an intracellular protein, the toxic tau variants are most likely generated intracellularly and will induce toxicity in neighboring cells intracellularly. An effective therapeutic for treating tau induced toxicity should selectively target the most toxic tau variants and should be able to do this both intra- and extracellularly. Here we will test our panel of six anti-tau nanobodies to identify which one has the most potent therapeutic benefit for potential human application. The nanobodies contain a C-terminal peptide tag that facilitates transport across the blood brain barrier and also enable transport into and out of neurons. The two most promising anti-tau nanobodies identified from this study using hiPSCs will be the focus of future in vivo studies using a tau AD mouse model. The final target nanobody be readily converted to IgG format for dosage, toxicity and biodistribution studies to prepare for an IND application. We have previously verified that the nanobodies in IgG format maintain their specificity and ability to inhibit tau toxicity, so we have already demonstrated the feasibility of each subsequent step of this project.

**Year End Progress Summary:** We are generating expression vectors to express six different antibodies targeting different toxic, AD associated oligomeric variants of tau. To identify the most promising tau based therapeutic for AD, we need to identify the variants of tau that occur during early stages of AD before significant neurodegeneration takes place. We utilized Braak staging to approximate progression of AD in human AD brain. We stained human medial cortex brain tissue with our panel of tau antibodies to identify which ones bound neurons in early Braak stage AD brain tissue but not in age matched controls. We identified three different novel anti-tau antibodies that we generated in our lab that preferentially bind a high percentage of neurons in Braak stage I and II tissue, but not in healthy controls. We also showed that phosho-tau antibodies primarily bind late stage Braak tissue, and primarily in neurofibrillary tangles. We also showed that our novel tau antibodies are present in blood samples of human AD cases early during disease progression, even in blood samples presymptomatically. Therefore we have identified three novel anti-tau antibodies that have potential therapeutic value to treat AD very early during disease progression before neurodegeneration has progressed very far. We are currently pursuing additional funds to develop these antibodies as potential therapeutics for early treatment of tauopathies.

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Injury-Induced Autoantibodies as Biomarkers for Alzheimer's Disease.** Sarah Stabenfeldt, PhD, Chris Diehnelt, PhD. Arizona State University; Arizona Alzheimer's Consortium; Robust Diagnostics, LLC, Phoenix, AZ.

**Specific Aims:**

1) Specific Aim 1: Develop and validate an autoantibody microarray platform with TBI specific biomarkers in preclinical model (mouse). Here, we will develop and validated a microarray platform to assess the autoantibody (aAb) profile of key TBI biomarkers (GFAP, NFL, and MBP). We will partner with Dr. Chris Diehnelt of Robust Diagnostics, LLC, who has developed a peptide array to map the epitope landscape of multiple sclerosis (MS). We will design an antigen panel for GFAP, NFL, MOG, PLP1 and MBP then validate panel of markers using a pre-clinical mouse model of TBI (controlled cortical impact). This platform has high potential for translation as it only requires a small drop of blood for each microarray panel (<5uL). Blood samples will be collected from a longitudinal cohort of mice over 1 month post-injury.
2) Specific Aim 2: Characterize the aAbs profile via microarray over time with respect to AD/ND pathology in TBI model. In our past AAC and NIH funded projects, we demonstrated heightened AD/ND pathology in weeks to months after TBI in our mouse model (see Preliminary Data). Here, we will characterize and correlate the aAb profile over 6 months post-injury with hallmarks of AD/ND, focusing on TDP-43 pathologies. A longitudinal mouse cohort will be followed for 6 months with autoantibody profiles assessed monthly post-injury. At month 6, the mice will be sacrifices an assessed for histological and transcriptomic makers of AD/ND. The results from this study will determine whether aAB profiles may provide prognostic and diagnostic insight to AD/ND.

**Background and Significance:**

An increased risk for Alzheimer's disease (AD) and neurodegenerative disorders (NDs) following a documented traumatic brain injury (TBI) has been identified in the clinic [1,2] and AD- like pathology has been observed in preclinical TBI models [3–5]. Studies of military personnel have identified TBIs as an independent risk factor associated with an up 60% increased risk of developing dementia [2,6]. Commonalities exist between TBI and AD/NDs pathologies [9–11], yet, the direct connection and potential contribution of TBI to AD/NDs pathologies remains elusive. Therefore, understanding and elucidating the potential role of TBI-induced neurodegeneration would afford an opportunity to detect, prevent, and intervene early.
Detection of those with high risk for developing AD/ND is critical. Post-TBI, a subset of patients experience persistent, chronic dysfunction and develop chronic AD/ND. An evaluation of these patients' autoantibody (aAb) profiles revealed elevated levels compared to healthy controls [16,17]. Studies have shown also that a TBI event may induce increases in polyreactive IgM and class switching to IgG occurs for specific antigens. Prior has focused on evaluating general aAb profiles, yet the whole antigen immunoassays do not resolve epitope differences between patients. Measuring antibodies against specific epitopes can resolve reactivity differences between patients that whole antigen immunoassays cannot. Therefore, the objective of this study is to (1) develop and validate a microarray platform with TBI specific biomarkers in preclinical model (mouse), and (2) characterize the aAbs profile over time with respect to disease progression – specifically ND/AD pathology.

**Experimental Designs and Methods:**

Aim 1a: Development of autoantibody (aAb) microarray. Here, Dr. Chris Diehnelt will generate an antigen peptide panel unique to the epitope landscape of aAbs to GFAP, NfL, MBP, MOG, and

PLP1. Dr. Diehnelt established this microarray technology for MS specific aAbs antigens (including clinical patient data) and has an established company on this technology, demonstrating high confidence in this approach and high potential for translation.

Aim 1b: Validate aAb microarray. Adult mice (equal mix of male/females) will sustain a unilateral CCI (IACUC approved). At the following timepoints, submandibular bleeding will be used collect a drop of blood (~25uL) for analysis: 3h, 1d, 3d, 7d, 14d, 28d, 2mon, 3mon, 4mon, 5mon, and 6mon post-injury. At each time point, blood samples will be collected via cheek bleed. At 6 months, animals will be sacrificed, blood samples will be collected followed by perfusion for RNA sample collection or IHC sample prep. The experimental groups will be CCI and naïve for each sex (n = 6 per group), thereby 2 injury conditions x 2 sex x 6 = 24 mice. Blood samples will used to validate the microarray. The brain tissue collection will be used in Aim 2.

Aim 2: Characterize the aAbs profile via microarray over time with respect to AD/ND pathology in TBI model. Dr. Stabenfeldt's team will lead the tissue and molecular analysis for the brain samples collected 6 months post-injury. Briefly, brains will be processed, sectioned, and mounted for IHC assessment. IHC analysis will be performed to determine TDP-43 pathologies described in preliminary data. Specifically, comparative metrics will be observed for human relevant markers of TDP-43 pathologies; mislocation of TDP-43, cytosolic accumulation of TDP- 43, hyperphosphorylation of TDP-43, and ubiquitination of TDP-43. Quantitative comparisons will be made of all metrics and correlated to the autoantibody profiles determined in Aim 1.
Statistics: Group sizes of 6 animals provide sufficient material and replication for histological analysis based on previous studies. Data will be analyzed by one-way ANOVA between timepoint groups and two-way ANOVA within timepoint groups to achieve 80% power in detecting a 20% change based on treatment at a $p<0.05$ level. Post-hoc analysis will be performed as necessary.

**Proposed One-Year and Long-Term Outcomes:**
The results from this study will determine whether tracking autoantibody (aAb) profiles after TBI may provide prognostic and diagnostic insight into AD/ND pathology. Data and findings from this proposal will be disseminated at national conferences and journal publications. The potential future outcome of the proposed AD/ND diagnostic tool will address injury-induced AD/ND early after injury thereby reducing AD/ND risk for millions. This project is very attractive for external funding agencies such as NIH, DOD, AAC, and American Federation for Aging Research.

**Year End Progress Summary:**
Aim 1a. aAb microarray development = 100% completed.
Dr. Diehnelt designed and fabricated the RobustDx aAb microarray composed of peptide regions from reported or likely aAb epitopes from multiple neurological protein targets (e.g., GFAP, NFL, MOG, PLP1, MBP, TDP-43). The array also included control peptides from human immunodominant epitopes from Epstein-Barr Virus (EBV), Cytomegalovirus (CMV), Herpes Simplex Virus-1 (HSV-1), and Herpes Simplex Virus-2 (HSV-2) to demonstrate species specificity for the mouse samples. A total of 60 different peptide epitopes were generated per microarray.

Aim 1b: Validate aAb microarray = 100% completed.
As a first test of antibody response specificity, we evaluated the binding of IgG from de-identified human samples (n=10) and 24 mouse samples from the day 28 post-injury cohort for binding to immunodominant epitopes from Epstein-Barr Virus (EBV), Cytomegalovirus (CMV), Herpes Simplex Virus-1 (HSV-1), and Herpes Simplex Virus-2 (HSV-2). Each peptide was significantly higher in human samples than mice, as expected, and exhibit seropositivity as expected rates in the US population. This result indicates that microarray and blood mouse samples processed exhibited low non-specific binding to human control epitopes.

Aim 2: Characterize the aAbs profile via microarray over time with respect to AD/ND pathology in TBI model.
We successfully completed a one-month mouse study to collect longitudinal blood spot samples after the controlled cortical impact (CCI). A total of 24 mice were used in the study with n = 6 per sex and naïve and injured groups. The dried blood spot samples from the day 28 post-injury were first measured for both IgG and IgM binding for each peptide on the microarray. The results indicated a number of significantly different IgM responses ($p<0.05$) across multiple neurological epitopes, particularly NfL and PLP peptides.

A feature of the RobustDx peptide array platform is the ability to profile antibody responses to wild-type (WT) and post-translationally modified (PTM) epitopes. Given the widespread phosphorylation changes reported in several potential aAb antigens, we included several peptides that contained phospho-Ser or phospho-Tyr modifications to search for aAb immunogenicity changes that occur with protein phosphorylation. In our preliminary studies, we have observed a differential aAb response in the pilot human sample cohort to a phospho-epitope from TDP43. A subset of samples exhibited an IgG clone that selectively recognizes the TDP43 phospho-epitope rather than the WT epitope while a different subset of samples reacted with the epitope independent of the phospho-status. This TDP43 epitope has 100% identity between human and mouse TDP43. For the mouse cohort, an IgM response was observed to both the WT and phospho-peptide only in the naïve mice. However, in the TBI mouse cohort, 0/12 mice react with the phospho-peptide and only 2 of 12 mice have IgM reactivity to the WT epitope. Neither the naïve or injured groups exhibited seroconvertion to IgG reactivity against either peptide. These data demonstrate the feasibility of studying immunological differences towards antigens that undergo phosphorylation and possibly other PTMs.

Utilizing the clinically relevant CCI mouse TBI model (injury centered over the primary motor cortex) in a non-transgenic mouse, we have recently discovered significant levels of TAR DNA Binding-Protein-43 (TDP-43) proteinopathies in RBFOX3 positive cells of the cortex rostral and distal to the injury site over 180 days post-injury. TDP-43 pathologies include nuclear mislocalization, hyperphosphorylation, and ubiquitinated cytosolic accumulations. TDP-43 pathologies are considered a hallmark in FTD and ALS cases, and are seen across a spectrum of NDs, including AD (prevalence 20-50% and up to 75% in severe cases of AD), FTD (prevalence ~50%), and ALS (prevalence >97%). TDP-43 is an RNA binding protein involved in a variety of processes, including RNA biogenesis and processing and the regulation of mRNA alternative splicing. Cell culture analysis has shown that when cleaved by caspase-3, the c-terminal fragment, TDP-35, co-localizes with stress granule markers predominately in the cytoplasm forming aggregates that lead to nuclear exclusion and alteration of RNA processing. Our analysis showed a significant increase in the levels of TDP-43 mislocalization in RBFOX3 positive cells throughout the study in both the cortex and the cervical spinal cord.

Proposal submissions: Our team submitted an R21 entitled, “Autoantibody profiling for TBI and neurodegenerative diagnostics” in July 2023; the proposal was scored with impact of 60 and 55 percentile. We resubmitted the A1 in March 2024; the proposal had an improved impact score of 50 and 43rd percentile. We will submit a revised application for the July/October 2024 cycle.

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Guidance of Learning and Reversal Ability by Neural Complexity in Cognitive-Associated Brain Regions of Juvenile and Middle-Aged Mice.** Jessica Verpeut, PhD, Heather Bimonte-Nelson, Ph.D. (President's Professor, Psychology Department). Arizona State University; Arizona Alzheimer's Consortium.

**Specific Aims:**

The specific aim of this project is to determine how neural complexity (i.e. dendritic structure and spine morphology) guides learning and reversal ability in juvenile and middle-aged male and female mice. Neurons in cognitive-associate brain regions will be analyzed post-task to understand relationships between cortical structure and cognition in aging.

**Background and Significance:**

The risk of dementia-related illnesses is estimated to be 2 out of 100 individuals aged 65-69. As the population ages, there will be a substantial challenge to both the healthcare industry and labor force. There is a critical need to study how age-related neural pathways change and why cognition wanes across the lifespan in different ways for males and females. While females are more likely to be diagnosed with Alzheimer's disease, males are at a greater risk for vascular dementia, but there is a deficit in research studying the female brain. Understanding sex-dependent trajectories in cognition and brain changes with aging and Alzheimer's disease is critical to discovering novel mechanisms driving these effects, as well as new therapeutics. Both estrogens and androgens have been suggested to be neuroprotective, as decreases in these levels have been associated with impaired memory, spatial, and verbal abilities (Kenny et al. 2002; Faubion et al. 2015). Brains of aged animals have decreased (28-43%) total spine number (Page et al. 2002; Duan et al. 2003; Kabaso et al. 2009) and reduced gray matter volume (De Bondt et al. 2013). My collaborator, Dr. Bimonte-Nelson, and others have found that surgical ovariectomy in rodents impairs cognition, reduces spine density and cortical thickness, and reduces miniature excitatory postsynaptic potential (EPSP) frequency (Ye, Cudmore, and Linden 2019; Koebele et al. 2017; Bimonte-Nelson, Bernaud, and Koebele 2021). We hypothesized that juvenile mice will exhibit superior performance to middle-aged mice, due to increased neural complexity and spine numbers, which will be found to be reduced in middle-aged animals.

**Preliminary Data, Experimental Design and Methods:**

The preliminary data to support this project analyzed juvenile (postnatal day 21) versus middle-aged (10 months of age) male and female C57BL/6J mice. Animals were trained to discriminate between two shapes on a digital touchscreen. The pairwise touchscreen task has high translational value, as it has been previously used to assess learning and reversal in rodents, non-human primates, and humans (Izquierdo et al. 2017). The correct shape is paired with a liquid reward of 20% sweetened condensed milk. In our preliminary results, reversing the correct shape resulted in deficits in correct choice performance in middle-aged compared to juvenile mice. In addition both male and female juvenile mice relearned the new correct shape faster compared to middle-aged same-sex mice.

Cognitive performance was assessed in C57BL/6J juvenile (postnatal day 21) and middle-aged (10 months old) mice using a visual discrimination touchscreen apparatus (Med Associates), see Table 1. From these animals, we collected brain samples per group/sex for analysis of neural

structure (dendritic complexity and spine morphology) in cognitive-associated brain regions, including the somatosensory cortex, medial prefrontal cortex, infralimbic cortex, anterior cingulate

cortex, and hippocampus. Brain tissue was analyzed using Golgi-cox methods. Dendritic complexity was assessed using Sholl analysis to measure number of branches, intersections, and distance of branches from the soma.

**Table 1: Experimental Design**

| Group | Number of males | Number of females | Age at testing onset |
|---|---|---|---|
| Juvenile | 12 | 12 | 21 days |
| Middle-aged | 12 | 12 | 10 months |

**Proposed One-Year and Long-Term Outcomes:**

Our laboratory maintains a colony of C57BL/6J animals and has both juvenile and mice aged to several months old for experiments to be completed by the end of the one-year project period. The lab has already collected preliminary behavior data in juvenile and middle-aged animals. It is expected that juvenile mice will have better cognitive flexibility compared to aged animals and task performance will positively correlate with neural complexity. In other words, animals completing more trials correctly will have more complex dendritic structures, spine numbers, and more mature spines. Mature spines are thought to be critical in learning and memory, therefore these numbers are expected to decline in aged animals and aged animals are expected to have less complex dendritic structures. All brain tissue samples will be quantified during this one year period and a manuscript will be written for publication. My undergraduate student, Vincent Truong, who has been leading this project, will be submitting an abstract to the Society for Neuroscience conference for a poster presentation in Washington D.C. and at the Arizona Alzheimer's consortium Fall 2023. This work will establish age-related changes in both males and females during the touchscreen visual discrimination task, which has not yet been assessed for these factors. It is anticipated that future work will test putative pharmacotherapies aimed to attenuate these age-related cognitive detriments in collaboration with Dr. Bimonte-Nelson and others. As well, this neurobehavioral model could be used to evaluate transgenic Alzheimer's disease rodent models to quantify changes in cognition, Alzheimer's disease-like pathology, and brain structure in comparison to the model's respective control population.

**Year End Progress Summary:**

One-year outcomes: Over the past year my lab has completed examining cognition in juvenile (P21, n=17 total), middle-aged (10 months, n=18 total), and a third group that underwent behavior analysis at juvenile and middle-age (n=16 total) We analyzed male and female C57BL/6J mice using the two-choice pairwise touchscreen task. To begin the task, animals are rewarded for interacting with the screen and quickly learn that touching the screen provides them with access to a dipper with 20% sweetened condensed milk. To continue through each shaping stage, animals have to increase the number of times they correctly interact with the screen. Once animals complete all shaping stages, they move on to visual discrimination (acquisition). During acquisition, mice only receive a reward when the correct shape is chosen, which is randomly shown on the left or right side of the screen. After animals meet criteria (70% correct trials across two consecutive days), the correct shape is reversed so the incorrect shape now will produce a correct trial and a reward.

Both juvenile and middle-aged animals were able to learn this task to criteria, but juveniles demonstrated significantly more correct choices during acquisition ($p<0.01$). While males and females did not differ in their acquisition learning rates, males had increased reversal performance in early learning (days 1-5) ($p<0.05$). In middle-aged mice, no differences were found between male and female learning rates. Compared to middle-aged mice, both male and female juveniles initiated and responded faster to trials during early stages of shaping and acquisition ($p< 0.001$),

as well as, collected rewards faster during reversal ($p<0.05$). When we analyzed male and female mice across time (juvenile to middle-aged), we found male mice increased in their correct choice performance during acquisition as they aged, while female mice demonstrated a decrease ($p<0.05$). Interestingly, there were no changes in reversal ability, but there was large variation found in female mouse correct choice performance. This variation may be a result of changes in hormone concentrations during this time period (10-12 months old) as the estrous cycle wanes. Lastly, we analyzed neural complexity and spines in multiple regions of juvenile and middle aged brains post sacrifice using Golgi staining and Sholl analysis (Figure 1). We found aged animals have reduced complexity compared to juvenile brains in the somatosensory cortex ($p=0.039$). Currently we are analyzing various additional brain regions, including the medial prefrontal cortex, infralimbic cortex, anterior cingulate cortex, and hippocampus for changes in dendritic complexity and spine number.

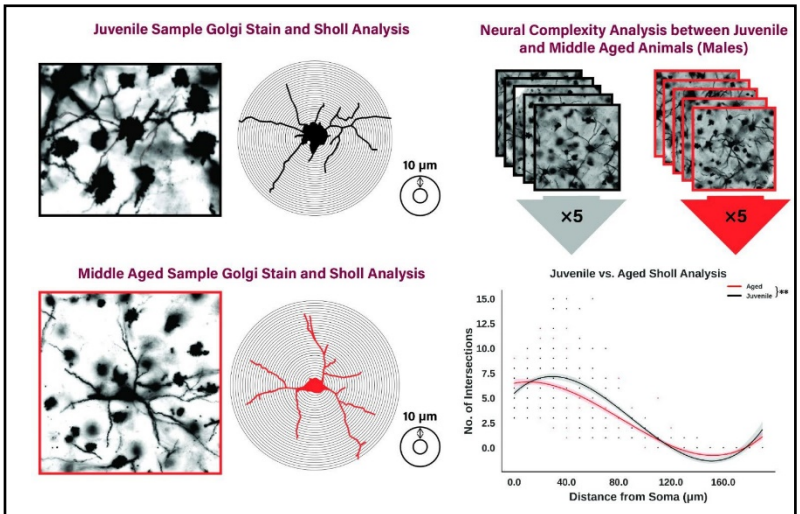



Figure 1. Examples of Golgi stained brains in juvenile (black) and middle aged (red) samples with Sholl Analysis. Differences were found between juvenile and middle aged samples in the somatosensory cortex ($p<0.01$).

The current work establishes age-related changes in both males and females on the two-choice pairwise touchscreen task and effects on neural structure. Future experiments will analyze changes in brain structure in Alzheimer's disease models. This work was foundational for a number of grant funding obtained and submitted this year. My undergraduate student, Vincent Truong, was awarded the Undergraduate Research Grant from Psi Chi (The International Honor Society in Psychology) and I received the AAC DHS Pilot grant (Co-Is Scott Beeman and Sydney Schaefer). Work from this grant supported pilot data for a NIH R01 and a HHMI application to the Freeman Hrabowski Scholars program.

Long-term outcomes: Neural structure analysis, as discussed in this update, will be completed by September for manuscript submission (authored by two undergraduate students). While the manuscript is in review, the data will be presented as a poster at the Society for Advancement of Chicanos/Hispanics & Native Americans in Science (SACNAS), the Society for Neuroscience in Chicago, and the AAC conference.

Challenges encountered: We found large variations in cognition across middle-aged female mice and in the future will take vaginal swab samples to understand relationships between cognition and hormones.

Future grant applicants and collaborations: This work will be preliminary data for a grant application studying aging with Heather Bimonte-Nelson, Sydney Schaeffer, and Scott Beeman. As a team, we are submitting a second R01 to NIDA this Fall 2024.

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Enhancing Low-Quality Retinal Fundus Images for Alzheimer's Disease Research.** Yalin Wang, PhD, Oana M Dumitrascu, MD, Yi Su, PhD, Eric Reiman, MD, Richard Caselli, MD, Kewei Chen, PhD, Bryan K Woodruff, MD, Simona Nikolova, PhD. Arizona State University (SCAI); Mayo Clinic Arizona; Banner Alzheimer's Institute.

**Project Description:**

Alzheimer's disease (AD)-related dementia (ADRD) is a significant public health concern, affecting 6.2 million Americans and costing US ~$239 billion in 2021. These numbers are expected to grow to nearly 50 million and $1.1 trillion by 2050. Current evidence supports that AD prevention at the preclinical phase before symptom onset is likely the most effective but will require the establishment of sensitive and cost-effective biomarkers to identify high-risk individuals and serve as endpoints for AD/ADRD randomized controlled trials (RCTs). The retina is a central nervous system organ that exhibits vascular changes, amyloid and tau deposition, and inflammatory and neurodegenerative changes that correlate with the "A, T, N, I" AD brain. The retina has the advantage of being more accessible for repeated and high-resolution imaging. Hence retinal imaging in the form of non-mydriatic retinal color fundus photography (CFP), has emerged as a non-invasive, cost-effective tool for studying AD. Although numerous studies have been devoted to discovering retinal imaging biomarkers for AD, there is a lack of dedicated retinal image screening tools for preclinical AD. Additionally, CFP image collection is prone to poor quality due to operators, systemic imperfections, or patient-related causes. That hinders the adoption of DL methods and precludes the analysis of millions of existing CFP images in AD research.

**Specific Aim**:

To develop unsupervised learning-based retinal imaging enhancement tools for mapping low-quality CFPs to high-quality counterparts. We will further improve the system's flexibility and robustness with a model-based image reconstruction method.
(a). Develop an optimal transport (OT)-guided generative adversarial network (GANs)-based unsupervised learning method coupled with regularization by enhancing; (b). Develop/test the system with multiple publicly available CFP datasets and validate it using locally generated (Arizona Alzheimer's Disease Research Center – ADRC) and independent data (UK Biobank). Hypothesis: Our system will enhance image quality and benefit AD research better than prevailing standard CFP analysis techniques.

**Background and Significance:**

Alzheimer's disease (AD) is a growing public health concern. In the United States alone, it is estimated that 14 million individuals will be affected by 2050. One reason for the lack of success in AD therapies is that they are often initiated too late or target non-AD causes. Early intervention with brain biomarker measurement shows promise for improving the likelihood of successful treatment. Aβ plaque and tau deposition are the hallmarks of AD and appear in the preclinical stages. However, studies have shown that a significant number of individuals with mild AD symptoms (as per clinical criteria) do not have detectable levels of Aβ. Therefore, developing advanced brain biomarkers to improve screening efficiency will benefit AD randomized controlled trials and expedite AD treatment development.

According to the A/T/N hypothesis, an early imbalance between Aβ production and clearance is followed by the accumulation of tau protein tangles, which together cause damage to the brain in the form of neurodegeneration. While assessment of Aβ/tau pathology using cerebrospinal fluid

(CSF) or positron emission tomography (PET) scans is well-established, these methods can be costly, invasive, and difficult to access. Blood-based biomarkers (BBB) are a more affordable alternative, but their clinical usefulness is limited by measurement variability. The retina has the advantage of being more accessible for repeated and high-resolution imaging. Hence retinal imaging has emerged as a safe and non-invasive tool for studying cognitive disorders. Recent research, including ours, has demonstrated that deep learning approaches may automate retinal feature identification, with the potential for translation into routine clinical practice. However, patient and provider-friendly, non-mydriatic retinal CFP is prone to noise, e.g., shading artifacts and blurring because of light transmission disturbance, defocusing abnormal pupils, or suboptimal human operations, resulting in low-quality CFPs. CFP degradation, such as obscuration of blood vessels, and missing or artifactual new lesions, leads to inaccurate diagnostic interpretation. Enhancing low-quality retinal CFPs into high-quality counterparts is of key importance for many downstream tasks. The lack of efficient CFP-enhancing tools results in a huge sacrifice of untapped information, which we will remedy in this project.

**Preliminary Data, Experimental Design and Methods:**

Deep Learning Application in Retinal Imaging Classification of Alzheimer's Disease. We proposed a deep neural network structure to discover potential AD biomarkers in CFPs. In our preliminary result, the dataset used for the downstream of training and testing derived from AD patients from Mayo Clinic, and normal control (NC) controls from the Eyepacs dataset. We evaluated the model by AUC-ROC curve and heatmap. Our trained model achieved an area under the ROC curve of 0.938 on the testing set, which represents the ability of the model to classify AD correctly. Meanwhile, the downstream task heatmap via Grad-CAM at the last convolutional layer demonstrated that the network mainly pays attention to the medium or distal retinal vascular branches in AD cases, whereas large vessel branches close to the optic disc head are highlighted in NC. Overall, our proposed network identified retinal blood vessel branches with tortuosity change as the potential identifier of AD and demonstrated the feasibility of AD diagnosis.

Experimental Designs and Methods. We will develop an integrated unsupervised end-to-end image enhancement framework based on optimal transport (OT) and regularization by denoising (RED) methods. We aim to address two challenges with existing unsupervised approaches: over-tampering of vessel and lesion structures and scarcity of training data. To solve the first problem, we will introduce a novel OT formulation with information-preserving consistency to prevent lesion and structure over-tampering. For the second problem, we will introduce RE, which requires less training data and will improve the flexibility, robustness, and applicability of the system.

**Proposed One-Year and Long-Term Outcomes:**

We expect to publish 3-4 joint journal papers during this funding period. With the preliminary results accumulated from this project, we plan to submit an NIA R01 grant in July 2023.

**Year End Progress Summary:**

*OTRE: Where Optimal Transport Guided Unpaired Image-to-Image Translation Meets Regularization by Enhancing* Our novel OT formulation maximally preserves structural consistency (e.g., lesions, vessel structures, optical discs) between enhanced and low-quality images to prevent over-tampering of important structures. To further improve the flexibility and robustness to images from different distributions and applicability in real clinical practice where no sufficient data is available to train the model, we will refine the enhanced images by our proposed regularization by enhancing (RE), a variant of RED method, whose priors are learned by the OT-guided network. We conducted extensive experiments in scenarios where the ground-truth clean images are available (full-reference assessment) and unavailable (no-reference assessment). Three downstream tasks including DR grading, vessel segmentation, and lesion

segmentation, were studied to further evaluate the performance of our proposed method. Visual inspection was conducted by human ophthalmologists to evaluate the performance of no-reference assessment. Our proposed method was extensively evaluated on three publicly available retinal CFP datasets: the EyeQ dataset, the DRIVE dataset, and the IDRID dataset. The EyeQ dataset was manually labeled into three quality levels: good, usable, and reject. We used 7886 training images and 8161 testing images (good & reject) in our training and evaluation. The DRIVE dataset evaluated our proposed method on the vessel segmentation task with 40 subjects. The IDRID dataset containing 81 subjects with pixel-level annotation of microaneurysms (MA), soft exudates (SE), hemorrhages (HE), and hard exudates (EX) were used to evaluate our method on DR lesion segmentation. The experimental results demonstrated the superiority of our proposed framework over some state-of-the-art unsupervised competitors and a state-of-the-heart supervised method.

*Context-Aware Optimal Transport Learning for Retinal Fundus Image Enhancement* The fundus image enhancement is typically formulated as a distribution alignment problem, by finding a one-to-one mapping between a low-quality image and its high-quality counterpart. We propose a context informed optimal transport (OT) learning framework for tackling unpaired fundus image enhancement. In contrast to standard generative image enhancement methods, which struggle with handling contextual information (e.g., over-tampered local structures and unwanted artifacts), the proposed context-aware OT learning paradigm better preserves local structures and minimizes unwanted artifacts. Leveraging deep contextual features, we derive the proposed context-aware OT using the earth mover's distance and show that the proposed context-OT has a solid theoretical guarantee. We validated the effectiveness of the proposed metho on three publicly available datasets: the EyeQ, DRIVE, and IDRID. Following our prior work, we trained the proposed method using the EyeQ dataset and evaluated it on the downstream tasks, such as vessel segmentation and diabetic lesion segmentation, using DRIVE and IDRID datasets. Experimental results demonstrate the superiority of the proposed method over several state-of-the-art supervised and unsupervised methods, including our OTRE work, in terms of signal-to-noise ratio, structural similarity index, as well as two downstream tasks. By enhancing image quality and performance in downstream tasks, the proposed method shows potential for advancing the utility of retinal fundus image-driven pipelines in routine clinical practice.

*A BERT-Style Self-Supervised Learning CNN for Disease Identification from Retinal Images* In medical imaging research, the acquisition of high-quality labels is both expensive and difficult. The introduction of Vision Transformers (ViT) and self-supervised learning provides a pre-training strategy that utilizes abundant unlabeled data, effectively alleviating the label acquisition challenge while broadening the breadth of data utilization. However, ViT's high computational density and substantial demand for computing power, coupled with the lack of localization characteristics of its operations on image patches, limit its efficiency and applicability in many application scenarios. We employ nn-MobileNet, a lightweight CNN framework, to implement a BERT-style self-supervised learning approach. We pre-train the network on the unlabeled retinal fundus images from the UK Biobank to improve downstream application performance. We validate the results of the pre-trained model on Alzheimer's disease (AD), Parkinson's disease (PD), and various retinal diseases identification. The results show that our approach can significantly improve performance in the downstream tasks. In summary, this study combines the benefits of CNNs with the capabilities of advanced self-supervised learning in handling large-scale unlabeled data, demonstrating the potential of CNNs in the presence of label scarcity.

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Comparison of Age-Related Responses to Menopause Variation on Brain Functioning: A Focus on Gene Expression in Reproductive and Brain Tissues.** Melissa Wilson, PhD, Heather Bimonte-Nelson, PhD (President's Professor, Psychology Department). Arizona State University; Arizona Alzheimer's Consortium.

**Specific Aims:**

The specific aim of this project is to study the molecular changes that occur in the uterus and the brain prior to and during menopause. Further, we will study how these changes correlate with behavioral differences across the same time period, using rodents from Bimonte-Nelson's corresponding project whereby animals were behaviorally tested after inducing variations in menopause. The research proposed here will support an ongoing collaboration with Dr. Heather Bimonte-Nelson to study the molecular mechanisms underlying memory changes associated with surgical reproductive tract manipulation, including ovariectomy (OVX). This work will set the stage for a larger NIH proposal to systematically determine brain- behavior-hormone-uterus relationships, a novel area of research first studied in the Bimonte-Nelson laboratory (Koebele et al., 2019)

**Background and Significance:**

Sex disparities in health increase with age (Carmel 2019), but the molecular mechanisms underpinning these are not well understood. Notably, sexual dimorphism in immune function appears as a general feature of many species, with differences documented across vertebrates and invertebrates, though at varying magnitudes (Nunn et al. 2009). Across a number of vertebrate species, there is evidence of female bias in the peripheral abundance of markers of innate and adaptive immunity (Fish 2008). In mammals in particular, both sex chromosome complement, as well as hormone levels, have been implicated in the female bias in disease prevalence (Klein and Flanagan 2016). Female mammals (e.g., rats, mice, humans) go through significant hormone transitions during aging.

It is well-documented that ovarian hormones, particularly estrogens, impact cognitive processes. Estrogens have long been considered to have neuroprotective properties, as well as beneficial effects on other body systems, such as bone and cardiovascular health. The loss of ovarian hormones has been reported to coincide with memory detriments in humans (Farrag et al., 2002; Nappi et al., 1999; Rocca et al., 2007, 2009, 2011, 2012), and also in rodent models (Bimonte and Denenberg, 1999; Talboom et al., 2008; Wallace et al., 2006). Recently, the Bimonte-Nelson laboratory has identified unique cognitive changes following manipulation of surgical menopause status, including with hysterectomy (Koebele et al., 2019). In the current proposal, we will address not only putative neurobiological changes that correspond to these behaviors as a result of reproductive status manipulations, but we also seek to determine potential changes within the uterus. Such knowledge is of critical importance to determining how the brain and uterus might interact following modulation of ovarian and uterine status. Thus, we are collaborating with Dr. Bimonte-Nelson on a sister project to characterize potential molecular alterations in uterine tissue and in brain regions critical to learning and memory. Our contribution to this interdisciplinary project will be to investigate the molecular changes (via RNA analysis) in both the uterus and the brain that may be underlying mnemonic changes.

**Year End Progress Summary:**

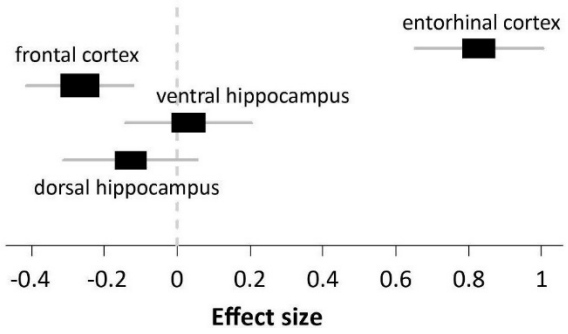
In the previous reporting period, we described how we conducted bulk RNA sequencing (RNAseq) on uterine tissue in a model of ovariectomy as a proof of principle of our ability to generate and analyze RNAseq data in collaboration with the Bimonte-Nelson lab. Gene expression profiling

demonstrated clear and marked changes in gene expression after removal of the ovaries. Genes that had significantly higher expression in rats with ovaries removed included estrogen repressed genes, and are enriched for genes involved in development of the nervous system, secretion and export from cells, and response to growth factors. Genes that had significantly lower expression in rats with ovaries removed included estrogen induced genes and are enriched for genes involved in the immune system, inflammatory response, cell cycle, and extracellular matrix organization. We also identified genes that had correlations with learning scores on a complex spatial working and reference memory maze task in rats with versus without ovaries.

In the current reporting period, we conducted RNA sequencing in the same ovariectomy model to measure gene expression in four regions of the brain that are associated with learning and memory and analogous to regions affected in Alzheimer's disease: frontal cortex, entorhinal cortex, dorsal hippocampus, and ventral hippocampus. We found subtle differences in the gene expression profile of ovariectomized subjects. We observed that gene expression profiles of the brain samples clustered by brain region; therefore, we conducted differential expression analysis between samples with and without removal of the ovaries in each brain region separately. We found that the entorhinal cortex showed the largest number of differentially expressed genes, more than double the number found in the other regions assayed. Effect size was calculated using covariance between all four brain regions (multivariate adaptive shrinkage analysis), demonstrating that the entorhinal cortex showed the largest effect with ovarian removal, and had changes in the opposite direction as the frontal cortex and dorsal hippocampus.

**Differential expressed genes and effect size in brain regions after ovariectomy (OVX) .** Genes differentially expressed between OVX and sham controls in each brain region demonstrated that the greatest differences were observed in the entorhinal cortex. Effect size was estimated utilizing covariance between all four brain regions.

| Brain Region | Number of differentially expressed genes |
|---|---|
| Entorhinal cortex | 1031 |
| Frontal cortex | 332 |
| Dorsal hippocampus | 307 |
| Ventral hippocampus | 167 |




**Proposed One-Year and Long-Term outcomes:**

In the next reporting period, we will be conducting analyses to further mine gene expression data from the uterus and brain to find specific categories of genes (and protein products) that could represent mechanisms for affecting learning and memory. We will use literature searches and gene function databases to identify specific subgroups of genes differentially expressed in the uterus and/or brain including: (a) secreted genes (proteins), as changes in secreted proteins after ovary removal might lead to a change in circulating blood and thus cause systemic changes to the nervous system and other systems, (b) known targets of hormone receptors, as these represent a direct mechanism of response to depletion of ovarian hormones, (c) genes known to regulate neurological pathways involved in learning and memory, (d) inflammation and immune genes, as inflammatory mediators are known to effect on memory, neural plasticity and neurogenesis. We will also use cell type deconvolution to determine if OVX correlates to changes

in the inferred proportions of specific cell types in each of the brain regions assayed. All gene expression and cell type proportion features will be correlated to learning and memory phenotypes to assess which features may be linked to cognitive phenotypes.

# BANNER ALZHEIMER'S INSTITUTE - PHOENIX
# PROJECT PROGRESS REPORTS

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Advanced Imaging and Data Analysis 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, Wendy Lee, MS, Kewei Chen, PhD, Yalin Wang, 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 including robust and high throughput analysis pipelines that allow large scale data analysis and facilitate trial planning.
2) Service AAC and the broad scientific community through data and analytical tools sharing.

**Background and Significance:**

Alzheimer's disease (AD) is a devastating disease affecting millions of families and putting significant burden on the society. With decades of research, we now recognize AD as a complex disease characterized neuropathologically by extracellular amyloid accumulations and intracellular tangles of hyperphosphorylated tau protein with strong influence from genetic factors. Imaging plays an important role in the characterization of AD and related dementia by providing in vivo measurements of amyloid and tau pathologies as well as other AD related changes of the brain such as reduction in glucose metabolism, inflammatory microglia activation, synaptic density changes, and global and regional brain structural changes that can be measured and monitored in vivo using either PET or magnetic resonance imaging (MRI). The ever-expanding imaging and multi-omics datasets call for the development of advanced analytical approaches that can leverage these datasets to improve our understanding of AD and ADRD and facilitate the development of effective treatment and prevention strategies. The Computational Image Analysis program at BAI and our collaborators have a long history of developing advanced statistical and analytical methodologies to advance AD and neuroscience research. Our team will continue this effort in this project year.

Given the devastating impact of AD and its increasing prevalence, there is an urgent need to accelerate the evaluation of promising drug and non-drug prevention therapies including those early phase trials that may inform larger and more expensive late phase trials. However, the use of conventional cognitive or clinical endpoints in the evaluation of potentially promising but unproven therapies has been a roadblock in the search for prevention therapies as these type of outcome measures requires large sample sizes and lengthy trial duration. Alternatively, biomarker from imaging, CSF, and blood can be measured quickly and objectively, and if a treatment's biomarker effects are associated with a clinical benefit in ongoing clinical or preclinical AD trials, it may be possible to find and support the accelerated regulatory approval of the same prevention therapy in unimpaired Aβ-positive persons using those biomarkers as "surrogate endpoints" that are found to be associated with a clinical benefit in recently completed or ongoing pivotal trials. In this project, we will continue to investigate various biomarkers and determine their ability to serve as such surrogate endpoints in clinical trials.

**Experimental Design and Methods:**

**Aim 1**: 1) We will further develop and implement imaging and data analysis pipelines and workflows leveraging our collaboration with the Gates Venture Imaging Platform team to further enhance our data management and analysis capabilities. 2) we will continue to investigate advanced image analysis techniques such as graph theory-based approach in tau PET longitudinal analysis as well as its application in other patient population such as CTE. 3) We will continue our collaboration with Dr. Yalin Wang's team on advanced MR image analysis

techniques. 4) we will leverage datasets such as ADNI and API-ADAD to facilitate efforts on future trial planning.
**Aim 2**: We will work closely with the DMSC core of Arizona ADRC and facilitate the sharing of the derivative imaging data our lab generated through our integrated and standardized pipelines from multiple cohorts including ADNI, Arizona APOE, and Arizona ADRC.

**Proposed One-Year and Long-Term Outcomes:**
For Aim 1, we will continue our imaging analysis methodology and pipeline development efforts to generate high-quality image analysis results for local and publicly accessible cohorts and support our team members and collaborators in their manuscript preparation.
For Aim 2, we will provide regular data release of image analysis results from our ongoing analysis efforts.

**Year End Progress Summary:**
In the past project year, the Computational Image Analysis team continued our efforts to develop, maintain, and implement advanced image and data analysis techniques and facilitate data and tool sharing.

For Aim 1, our continued development and maintenance of image analysis pipelines focused on the integration of multiple MRI tools into a streamlined process that aligns individual MRIs with a common template and achieves highly accurate within-subject alignments to enable and facilitate cross-sectional and longitudinal data analysis; standardizes and harmonizes of structural MRI data from multi-center studies and across different cohorts; integrates widely used structural MR analysis tools including FreeSurfer and SPM; conversion of PET imaging data from different format, e.g. DICOM and ECAT, into commonly adopted neuroimaging format, NiFTI, while preserving important metadata such as the timing of the image acquisitions, the injection dose, and the decay correction information; streamlines automated PET image analysis to reduce scanner resolution differences, align with MRI reference images and anatomical atlas, extract regional measurements with and without accounting for the low spatial resolution of PET, and generate parametric maps. As part of our continued development and validation of image analysis techniques, we recently determined that current standardization techniques to account for multi-center, across cohort studies are still inadequate and will continue to develop more advanced techniques to address this challenge. As part of our collaboration with the Gates Venture-sponsored Global Research Imaging Platform (GRIP) initiative, we will incorporate our streamlined pipelines and workflows into the GRIP platform and make it available to the broad research community in the coming years.

Leveraging a recently developed graph theory-based approach for tau PET analysis, we examined the utility of this approach in the analysis of tau PET data from former American football players. Tau PET images from the DIAGNOSE CTE cohort were analyzed to construct individual tau PET graphs and derive graph theory-based measures. We found these measures can differentiate exposure groups similarly to conventional regional measures, while a specific measure using the graph theory approach, the entorhinal strength, was the only measure that could detect group-level differences between players with a consensus clinical diagnosis of traumatic encephalopathy syndrome from those who do not in participants over 60 years old. A manuscript is currently in preparation for submission as a journal article.

In our continued collaboration with Dr. Yalin Wang (ASU) and other collaborators, we continue to develop advanced image analysis techniques. In one of the developments, we proposed a surface-based hippocampal morphometry system to identify participants with elevated plasma NfL levels, a blood-based biomarker for neurodegeneration. We illustrated our technique performed significantly better than conventional approaches. We also demonstrated these morphometry measures combined with a proposed sparse coding-based classification algorithm can achieve an accuracy of 86% in differentiating cognitively normal participants with

and without elevated NfL levels. Both the group-level and individual-level analysis results indicate that the association between plasma NFL levels and the hippocampal shapes can be mapped at the preclinical stage (Dong et al. IEEE Transaction on Computational Social Systems 2023). In another development, we propose a self-supervised contrastive learning method to accurately predict the conversion to AD for individuals with mild cognitive impairment (MCI) with 3D amyloid-PET. The proposed method, Semi Momentum Contrast (SMoCo), uses both labeled and unlabeled data to capture general semantic representations underlying the images. As the downstream task is given as classification of converters vs. non-converters, unlike the general self-supervised learning problem that aims to generate task-agnostic representations, SMoCo additionally utilizes the label information in the pre-training. To demonstrate the performance of our method, we conducted experiments on the ADNI dataset. The results confirmed that the proposed method is capable of providing appropriate data representations, resulting in accurate classification. SMoCo showed the best classification performance over the existing methods, with an accuracy of 81% (Kwak et al. Bioengineering 2023).

We also continue to work with the Alzheimer's Prevention Initiative investigators to leverage ADNI and API-ADAD data to plan for future clinical trials of anti-amyloid therapy/prevention strategies and contributed to a large planned clinical trial in Colombia Kindred of an inherited form of AD.

For Aim 2, our team continues to perform analysis of existing imaging dataset from different cohorts in addition to local ongoing studies including Arizona ADRC and Arizona APOE studies. As of now, we have processed a total of 29470 MRI scans, 6386 amyloid PET, 1765 Tau PET, and 3469 FDG PET scans across 10 different cohorts (including the two local cohorts). We are releasing the first imaging data freeze for Arizona ADRC data in June 2024 to all consortium investigators and will work collaboratively with investigators interested in other datasets we have processed and curated. We will also continue the image analysis and curation efforts in the coming years.

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Machine Learning and Artificial Intelligence in Alzheimer's Research.** Yi Su, PhD, Hillary Protas, PhD, Javad Sohankar, PhD, Dhruman Goradia, PhD, Ji Luo, MS, Shan Li, MS, Wendy Lee, MS, Yalin Wang, PhD, Kewei Chen, 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) To further develop and validate machine learning (ML) and deep learning (DL) techniques and their application in AD and aging research.
2) To develop ML and DL techniques for multi-omics data analysis.

**Background and Significance:**

AD is a complex disease with strong genetic influence and heterogeneous phenotypes. The ever-expanding imaging and multi-omics datasets call for the development of advanced analytical approaches that can leverage these datasets to improve our understanding of AD and ADRD and facilitate the development of effective treatment and prevention strategies. In recent years, there has been an increased adoption of ML and AI methods in the analysis of AD/ADRD datasets and the investigation of the diseases. Our team has also made substantial advances in this area in together without ASU collaborators. We will continue our momentum and further investigate ML/AI techniques in this project year focusing on the two aims.

**Experimental Design and Methods:**

**Aim 1**: a) We will further investigate the use of DL techniques for age prediction based on imaging data to better characterize both normal and pathological aging. We will also investigate the interpretability of the DL models to better understand the imaging characteristics and features that are associated with normal and pathological aging. b) We will investigate physics and biology-based generative models derived from large datasets to facilitate further development of ML/DL techniques and improve their application in neuroscience research. Such models will allow us to generate a large number of labeled imaging data with known ground truth that can help objective evaluation of model performance, augment model training, determine optimal hyperparameters, and subsequently allow us to build better performing DL models for a wide range of applications such as noise reduction, spatial resolution improvements, accurate quantification, and better harmonization. c) We will continue to investigate ML and DL techniques in applications such as the prediction of disease progression and differential diagnosis models based on multi-modality data.

**Aim 2**: We will further develop and apply ML/DL techniques to the analysis of multi-omics dataset to better characterize the underlying molecular mechanism of AD pathogenesis and progression and examine the quantitative phenotype-genotype relationship that can help establish personalized models of disease progression. We will continue to work with Dr. Wang and her team in the development and application of ML/DL models for the analysis of bulk tissue RNA-seq data to characterize the gene expression networks that are associated with and predictive of pathological burden and cognitive performance. We will also work with her team to explore the development and application of ML/DL models to snRNA-seq data to better understand the cell type specific gene networks implicated in AD's onset, manifestation, and progression.

**Proposed One-Year and Long-Term Outcomes:**

In the upcoming year, for Aim 1, we anticipate generating at least one manuscript and one abstract on the application of deep learning models in ADRD research. For Aim 2, we also anticipate generating a manuscript and a conference abstract as a result of the collaborative efforts.

**Year End Progress Summary:**

In this project, the BAI Computational Analysis team continues working with our ASU collaborators to develop and apply ML/AI techniques in AD/ADRD research. ML/AL techniques require large datasets to build models. Leveraging additional support from the separate AAC-funded Advanced Image Analysis project, we have over 20,000 T1-weighted MRIs and more than 5,000 PET scans processed using our standardized pipelines across major datasets including ADNI, NACC, AIBL, OASIS, and Arizona local cohorts. This large dataset is routinely used in our examination of ML/AL techniques.

For Aim 1a, leveraging the large MR datasets, we further improved our MR-based age prediction models, and one specific problem we focused on was the phenomenon known as regression to the mean (RTM) where the predicted age was biased towards the mean age of the population used for training, i.e. the predicted age was older than the true age on average for young participants and younger than the true age on average for older participants. The cause of this phenomenon is not fully understood but is commonly thought to relate to imbalanced training data, the nonlinear trajectory of the age-associated brain change, and survival biases. We hypothesized that this can be improved if we adopt a cost function that penalizes more on the prediction error towards the end of the age ranges and frame the age prediction as a classification problem, i.e. assign each participant to an age bin, instead of a regression problem, i.e. minimize the numerical difference between true and predicted age. To test this hypothesis, we used a combined dataset including NACC (N=4132), OASIS (N=1432), ICBM (N=1101), IXI (N=536) and ABIDE (N=176) to cross-validate and test. In addition, we used ADNI (N=1584) for the blind testing. Results show improved brain age prediction (MAE=2.56) compared to the conventional approach (MAE=4.57) while also reducing the bias.

For Aim 1b, we developed a simulation tool that generates simulated amyloid PET imaging data based on structural MRI data with the additional simulation of realistic tracer uptake profiles derived from real amyloid PET data. The simulation tool performs the simulation in two steps. In the first step, using MRI image and its derived brain tissue probability maps as the input, the tool generates a high-resolution map of PET tracer retention (the digital PET phantom). In the second step, using the high-resolution digital phantom, we simulate the PET imaging formation process computationally to account for the physical process of PET signal generation, detection, and image reconstruction to generate realistic simulated PET images. The anticipated use of this tool is to facilitate the development of AI-based image analysis tools. We recently generated 3,000 sets of matched MR and simulated PET data for two different PET tracers, and trained an AI model that enhances the spatial resolution of the PET images to facilitate between tracer harmonization. This work is ongoing and a manuscript is currently in preparation.

For Aim 1c, we continue to work with Dr. Yalin Wang's ASU team on applying ML/DL techniques to build predictive models using imaging data. In this work, structural information describing the shape and size of the hippocampus were derived from MR images and together with the blood-based biomarker, Aβ42/40, an ML model was trained to predict whether a participant has detectable amyloid pathologies in the brain. We evaluated the model performance using two distinct cohorts, one from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the other from the Banner Alzheimer's Institute (BAI), including prediction accuracy, precision, and area under the curve (AUC) score. Results from ADNI (mean age 72.6, Aβ+ rate 49.5%) and BAI (mean age 66.2, Aβ+ rate 36.9%) datasets revealed the integrated multimodal (IMM) model's superior performance over unimodal models. The IMM model achieved prediction accuracies of

0.86 in ADNI and 0.92 in BAI, surpassing unimodal models based solely on structural MRI (0.81 and 0.87) or plasma Aβ42/40 (0.73 and 0.81) predictors.

For Aim 2, we continue to work with Drs. Teresa Wu and Qi Wang on applying ML/AI techniques to analyze multi-omics data. The collaborative team recently developed an interpretable deep learning model for analyzing bulk RNA-seq data from three different brain regions in the Religious Orders Study and Memory and Aging Project (ROSMAP) cohort from the AMP-AD open data platform. The Shapley Additive exPlanations (SHAP) values, which have not been previously applied to dissect gene expression in AD, was used to interpret and obtain novel biological insights from the models. To test the generalization of our proposed framework, two independent AMP-AD datasets, the Mayo RNA-seq study cohort (MAYO) and the Mount Sinai Brain Bank (MSBB) study cohort were studied. The framework achieved superior performance in correlating expression profiles with both neuropathological and clinical traits and demonstrated unprecedented prediction accuracy. From model interpretation, we identified 1,317, 1,594 and 1,643 genes implicated in AD in the three brain regions respectively. We investigated the overlaps of these genes and compared them with the differentially expressed genes (DEGs) identified in the same AD versus control comparisons. We observed that our approach shows the potential to unveil non-linear gene regulation relationships that are obscured by bulk-tissue profiling, which would otherwise only be observable in single-cell RNA-seq data. From co-expression analysis, we identified the transcriptomic modules associated with microglia activation shared among brain regions and a region- and sex-specific transcription factor implicated in neuronal loss and linked with sexual dimorphism in AD3.

In addition to efforts supported by this project, our team also led/participated in investigations leveraging ML/AL techniques to improve imaging harmonization, enhance multi-modal analysis, and construct predictive models in other funded projects (e.g. RF1AG073424, R01AG069453, R01AG055444, U54MD000507).

**Supported Grant Submissions:**

Deep learning approach on single nucleus RNAseq data towards understanding cell type specific gene regulations in Alzheimer's disease (Arizona ADRC Developmental Project, PI: Wang, ongoing)

Systematic investigation of genetic contributions of sex chromosomes to Alzheimer's disease (R21, PI: Wang, submitted March 2024)

Multi-Scale Modeling of Aging and Alzheimer's Disease. (R01, PI: Su, submitted June 2024)

**Publications:**

1. Shah J, Siddiquee MMR, Su Y, Wu T, Li B. Ordinal Classification with Distance Regularization for Robust Brain Age Prediction. IEEE Winter Conf Appl Comput Vis. 2024;2024:7867-76. Epub 20240409. doi: 10.1109/wacv57701.2024.00770. PubMed PMID: 38606366; PMCID: PMC11008505.

2. Chen Y, Su Y, Wu J, Chen K, Atri A, Caselli RJ, Reiman EM, Wang Y. Combining Blood-Based Biomarkers and Structural MRI Measurements to Distinguish Persons with and without Significant Amyloid Plaques. Journal of Alzheimer's Disease. (Preprint):1-12.

3. 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. bioRxiv. 2024:2023.12.18.572226. doi: 10.1101/2023.12.18.572226 (under review).

# ARIZONA ALZHEIMER'S CONSORTIUM
# 2023-2024 Scientific Progress Report

**Statistical and Neuroimaging Data Science Core Resources Serving Consortium Members.**
Yi Su, PhD, Michael Malek-Ahmadi, 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, Don Saner, MS, Eric M. Reiman, MD.
Banner Alzheimer's Institute; Arizona State University; University of Arizona; Mayo Clinic Arizona; 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 including Arizona APOE study, the Arizona ADRC, API-ADAD, ADNI, NACC, and other cohorts.
2) Offer comprehensive statistical, image analysis, and training services to investigators and students inside and outside Arizona based on the common interest and their needs.

## 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 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. We will closely work and support 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:**

In this funding year, for Aim 1, our team continues to curate harmonized datasets from our local cohorts including Arizona APOE cohort, Arizona ADRC cohort and API-ADAD. In conjunction with the Arizona ADRC DMSC core, we are providing monthly updates of the ADRC cohort imaging results and planning for the return of these results back to participants. Our team also expanded our collection of widely used cohorts such as ADNI and included additional cohorts including AIBL, OASIS1/2/3, NACC legacy MRI cohorts, IXI, and ICBM. This collection of additional datasets was processed using our standardized and streamlined analysis pipelines leveraging support from our Consortium supported Advanced Image Analysis project and is made available to Consortium investigators through collaborative research.

Investigators supported:
a) Dr. Craig Weinkauf (UA) to examine structural brain changes in relation to vascular risk factors leveraging the ADNI dataset we curated and processed.
b) Drs. Teresa Wu and Yalin Wang (ASU) develop advanced machine learning and AI techniques to characterize brain changes as a function of age and resolve technical confounds through advanced harmonization techniques.
c) Dr. Emily Edmonds (BAI-Tucson) to examine the structural-functional relationships to determine how cognitive performance is associated with structural brain variations.

For Aim 2, we also continued our effort to support investigators within and outside of our Consortium and provide mentorship to students with the following examples highlighted below:

In the past year, led by Dr. Malek-Ahmadi in collaboration with Dr. Sydney Schaefer at ASU, our team continued to support the joint effort to examine motor function changes in aging and AD and integrated Dr. Schaefer's motor task into the Longevity Study at BSHRI and the APOE study at BAI. In addition, our team also worked together with Drs. Schaefer and Beeman (ASU) and their graduate student Nelson Yamada, a pilot study was performed to examine how APOE genotype affects white matter integrity using data from the Arizona APOE cohort. This study confirmed that the presence of APOE4 allele has a detrimental effect on white matter integrity and also suggests the presence of the APOE2 allele may confer a protective effect on white matter integrity. The results were presented at the Consortium Scientific meeting in September 2024.

Dr. Malek-Ahmadi continues to serve as a Scholarly Project mentor with the University of Arizona College of Medicine-Phoenix where he assists medical students in their own data analysis projects. He has also mentored medical students from University of Arizona College of Medicine-Tucson and Midwestern University on research projects, several of which have been published in this funding cycle, leveraging meta-analysis techniques and generated 4 peer reviewed journal publications. Dr. Su also mentored an MD/PhD student, Ms. Vedanshi Bhargava (UACOM-P), who successfully defended her PhD dissertation in December 2023 and is currently working on at least two manuscripts for publication.

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 and generated two peer reviewed journal publications. Continue working with Dr. Suchy-Dicey (who recently moved from WSU to the Huntington Medical Research Institute), 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.

A list of projects and investigators supported by this award during this funding year included:

a) Dr. Quiroz (MGH), supporting her investigation of AD risk factors in autosomal dominant AD populations.
b) Dr. Suchy-Dicey (Washington State University), supporting her research of AD and aging in Native American population.
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 to his grant application efforts.
g) Dr. Fang Yu (ASU), continued collaboration and imaging/data analysis support to her non-pharmaceutical intervention studies.
h) Dr. Tseng (ASU), grant applications.
i) Dr. Leung (ASU), dog aging study.
j) Dr. Smith (John Hopkins), providing our multi-modal imaging data analysis for her late-life depression study including new MCI and longitudinal data.
k) UACOM-P students research projects.

Through the NIH funded ADRC DMSC core our team also supported:
a) The DIAGNOSE CTE study team, providing statistical and tau PET imaging analysis support to better characterize CTE/TES.
b) Dr. Banks (UCSD), investigating of sleep apnea and tau pathology in the DIAGNOSE CTE cohort.
c) DIAN team, investigating biomarker changes in autosomal dominant AD.
d) Dr. Benzinger's (WUSTL) team investigating PET imaging techniques.
e) Dr. Li's (Georgia Tech) team developing advanced deep learning techniques for AD diagnosis and prognosis.
f) A multi-institutional collaboration investigating genetically proxied angiotensin-converting enzyme (ACE) inhibition association with dementias.
g) Dr. Coleman (ASU) integrating DNA methylation and RNA profiling to investigate AD.
h) Dr. Joseph-Mthurin (WUSTL) investigating how the position of mutation on the presenilin-1 gene influences the phenotype of autosomal dominant AD.
i) Dr. Raichlen (USC) investigating sedentary lifestyle and dementia risk.

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 12 additional grant applications and over 30 publications. We anticipate continuing this effort to support Consortium and external investigators in the upcoming year.

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Native American Outreach, Recruitment, and Retention Program**. David Weidman, MD, Nicole Lomay, Lori Nisson, LCSW, Alireza Atri, MD, PhD, Eric M. Reiman, MD, Jessica B. Langbaum, PhD, Heather Mulder, David Coon, PhD. Banner Alzheimer's Institute; Banner Sun Health Research Institute; Arizona State University; University of Arizona; Arizona Alzheimer's Consortium.

**Specific Aims:**

1. To forge a close and dynamic working relationship with members of our Native American Community to raise greater awareness and appreciation of advancing clinical and scientific information about the management of Alzheimer's disease and related disorders (ADRD), through educational and service-related outreach activities in this underrepresented research population.
2. To support the work of the newly formed American Indian/Native American AD Research Advisory Committee's work to help establish policies related to Indigenous Data Sovereignty for our ADRC and affiliated studies.
3. To fulfill the mission that Native Americans are leading the way, to inform and advise researchers how they should use biologic data to advance the scientific understanding of Native Americans who may be at risk of developing symptoms of ADRD, while respecting cultural sensitivities of all tribal communities in Arizona.

**Background and Significance:**

Native Americans facing the problem of Alzheimer's disease (AD) constitute the most underrepresented and understudied population in the United States. Since 2006, we have established an outreach program to help address the educational and clinical needs of patients, families, and health care professionals; developed culturally sensitive educational and service programs; and demonstrated to the Native American communities our strong interest in serving these needs, whether or not they participate in research studies. Once we were able to put policies in place to ensure Indigenous Data Sovereignty, by establishing an American Indian/Native American AD Research Advisory Committee in 2023, we renewed our partnership with Medstar's Strong Heart Study locally. The committee is tasked with working with Native American Community Leaders to create an Indigenous Data Sovereignty and data sharing plan, to include the review and potential approval of future research studies.

**Preliminary Data, Experimental Design and Methods:**

More than 130 Native Americans have been enrolled into the Arizona Alzheimer's Disease Research Center (ADRC) Clinical Core across the consortium as of early June 2024; of those, more than 75 have their data uploaded to the National Alzheimer's Coordinating Center (NACC) database, the majority from the BAI-Phoenix study site. In October 2023, we resumed recruitment of new Native American participants, once we were able to put policies in place to ensure Indigenous Data Sovereignty. Formation and outline of responsibilities of the committee allowed the BAI-Phoenix site to renew its partnership with Medstar's Strong Heart Study locally. There are 51 actively enrolled Native Americans in the ADRC Clinical Core at Banner Alzheimer's Institute-Phoenix—an increase of 12 participants since the start of the 2023-2024 budget year.

An annual Conference on Native Americans and Alzheimer's disease would continue to be held, with a preconference intensive training for professional attendees representing several tribal communities, and a full day conference included professionals, family caregivers, community members, and persons with early Alzheimer's disease.

The Native American outreach team would continue to find innovative ways to reach tribal community members, including expanding BAI Native American Beacon e-newsletter distribution to human services, senior centers, and health care centers to augment accessibility. The team would hold a monthly Native American Circle discussion group, offering information and support to caregivers and community members from Arizona tribal communities. The team would design and print BAI Beacon "Spotlight Caregiver" articles, facilitate placements for persons with memory loss, and broadly distribute copies of the articles quarterly. Communities would continue to deliver meals to homes, and meal pick up programs within tribal nations across Arizona. The team also would connect with tribal families living with dementia to provide our comprehensive Native American Navigating Memory Loss guides.

Vital to the development of the American Indian/Native American AD Research Advisory Committee was the appointment of two experts as co-chairs: Cynthia West, managing director of MedStar Health Research Institute and an American Indian researcher, and Ginger Sunbird Martin, an American Indian leader in addressing healthcare disparities among indigenous people. The other Committee members include Grandmother Pershlie "Perci" Ami, Dr. Megan Christopher, Violet Mitchell-Enos, 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: extent of research involvement of individuals who identify as American Indian / Native American, but may not reside on Tribal land; how data and biological sample collection is shared with Tribes; how and when researchers may be allowed to use this data for scientific purposes. Their efforts may complement similar efforts at the national level.

**Proposed One-Year and Long-Term Outcomes:**

1. After Covid-19 restrictions during the Public Health Emergency were lifted in May 2023, more sustained and consistent outreach efforts to general Native American communities were achievable. Education of health care providers for American Indians--aiming to decrease the disparity related to diagnosis and treatment of AD and related disorders in both reservation and urban dwelling Natives—also improved, as pandemic-related health conditions/concerns became less demanding.
2. Supported the American Indian / Native American AD Research Advisory Committee's effort to develop policies related to Indigenous 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. Longer-term goals and outcomes would include generating scientifically valid studies to clarify the generalizability of plasma biomarkers compared to amyloid PET in this under-represented group, and to gain a better understanding of which genetic, lifestyle and health-related factors pose the strongest risks of AD and related neurodegenerative disorders in the NA/AI populations (which may differ from relative risks in more well-studied races and ethnicities participating in AD research in a far greater proportion)
3. Continue to maintain a relationship and retain the active Native American participants enrolled in the ADRC Clinical Core, at BAI-Phoenix. Continue to track new participant enrollment, to help ensure rate is adequate to increase the number of active participants and ultimately achieve the goals/outcomes described above, which may be feasible to accomplish focusing on Arizona's Native American participants. Continue to collaborate with other affiliated studies which offer under-represented groups including Native Americans the opportunity to participate in brain imaging studies.
4. Refine methods to reach more Native Americans from youth to elders to raise community awareness by offering quarterly virtual education programs.

a. Provide timely topics quarterly on brain health, dementia friends, research updates and dementia caregiver education.

b. Offer monthly digital BAI Native American Beacon newsletters and quarterly printed newsletters.
c. Collaborate with other core centers, to improve outreach strategies and improve awareness to enrollment pathway.
5. Increase national engagement, knowledge, and collaboration amongst clinicians and researchers treating Native Americans using data gathered through the study. Leverage available data for educational purposes at the annual Native American Conference in Alzheimer's disease.

**Year End Progress Summary:**

Aim 1: In October 2023, the team held the 17th Annual Conference on Native Americans and Alzheimer's disease at the Desert Diamond Casino and Conference Center in Tucson. The preconference intensive provided training for 62 professional attendees representing 15 tribal communities. The full day conference included professionals, family caregivers, community members, and persons with early Alzheimer's disease and hosted 209 attendees representing 18 unique tribes across Arizona as well as Idaho, New Mexico, North Carolina, Oklahoma, Texas, Washington, Wyoming, and Utah. The preconference intensive focused on Setting Families Up for Success and the full day program theme included Understanding and Overcoming Barriers for Care featuring topics on Understanding Dementia, Progression and Research opportunities, Managing Stigma in Dementia Care, Caregiver Self Care and the Grieving Brain.

The Native American outreach team continued to find innovative ways to reach tribal community members through the provision of a BAI Beacon Native American monthly e-newsletter distributed to more than 5800 professionals, family caregivers, and community members The team held monthly Native American Circle discussion group, offering information and support to 100 caregivers and community members from Arizona tribal communities. The team designed and printed BAI Beacon Spotlight Caregiver Articles featuring brain health and caregiver wellness tips and Native American Outreach activity placements for persons with memory loss and distributed 6000 copies quarterly as well as more than a dozen community home delivered meals and meal pick up programs within tribal nations across Arizona. We continued to train professional and family caregivers to use music to support people living with dementia, using our BAI Walk with Me CD, reaching 450 individuals this past year, and connected with tribal families living with dementia to provide our comprehensive patient caregiver guide, Native American Navigating Memory Loss.

Aim 2: Through the 2023-2024 budget year, 33 initial and follow-up assessments were conducted, no participants were withdrawn, and no deaths. We continued to work with the ADRC Education Core and collaborators from the Strong Heart Study, and our newly formed Native American Research Committee to enroll, retain, and study Native American participants in our in our longitudinal research program in highly productive ways that adhere to Indigenous Data Sovereignty Principles.

Funds was used in a way that complemented, but did not overlap, with funding provided by the National Institute on Aging (NIA, which supports some of our outreach and clinical core enrollment activities), from the May and Stanley Smith Charitable Trust, the John and Sophie Ottens Foundation, and a community partner, the Inter-Tribal Council of Arizona, Inc. – Area Agency on Aging, Region 8 (Grant ID: 90ADP10077-01-00)

# ARIZONA ALZHEIMER'S CONSORTIUM
# 2023 – 2024 Scientific Progress Report

**Scientific Support to Enhance the Alzheimer's Prevention Initiative.** Eric M. Reiman, MD, Pierre N. Tariot, MD, Jessica B. Langbaum, PhD, Robert Alexander, MD, Jeremy Pruzin, MD. Banner Alzheimer's Institute; University of Arizona; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

## Specific Aims:

1. To support efforts for a preclinical Alzheimer's disease (AD) trial/surrogate marker development program in cognitively unimpaired autosomal dominant (ADAD) mutation carriers within 15 years of their estimated age at clinical onset (i.e., the API ADAD Colombia Trial), analyze and share trial data, and plan for future trials in the kindred.
2. To support efforts to analyze data and samples and share trial data and samples from the API Generation Study 1 and Generation Study 2 trials.
3. To support clinical study planning efforts for a longitudinal observational study of individuals whose blood-based biomarker test makes them ineligible for Lilly's planned secondary prevention trial of remternetug to inform the design of future primary prevention trials.
4. To support clinical trial planning efforts for 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 genetic and biomarker results to individuals, leveraging the above-mentioned observational study and Lilly's planned secondary prevention trial of remternetug.
5. To support efforts for planning and securing 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.
6. To continue to support registries designed to assist with participant recruitment, including efforts to increase participant diversity and bolster registry infrastructure.

## Background and Significance:

Alzheimer's disease (AD) is the most common form of dementia. Results from observational studies suggest that the pathophysiological process of AD begins years, if not decades, before the diagnosis of clinical dementia. It is possible 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. We and others have shown how biomarkers could be used to detect and track the progression of AD, including in ADAD mutation carriers, providing a foundation for use in evaluating AD-modifying treatments(1). In 2009 we launched the Alzheimer's Prevention Initiative program. In May 2012, BAI was awarded a grant from the NIH to support a preclinical treatment trial of crenezumab in 300 PSEN1 E280A kindred members in Colombia; a second R01 grant was awarded in April 2017 to complete the trial, add tau PET to the trial at 30- and 60-month visits, and implement the data and sample sharing program. In September 2013, BAI was awarded a grant from the NIH to support a preclinical treatment trial of two anti-amyloid therapies from Novartis, an active immunotherapy (CAD106) and a BACE inhibitor (umibecestat), in a trial in approximately 1,300 APOE4 HM ages 60-75. Recruitment in the Generation Program and treatment with umibecestat was terminated in July 2019 after an early signal of mild worsening in some measures of cognitive function with umibecestat. In 2018, API and A4 leaders were awarded a grant from the NIA to help support a proposed prevention trial of an anti-amyloid therapy in cognitively unimpaired adults with elevated brain amyloid. Due to the decision not to proceed with a prevention trial of aducanumab and the discontinuation of the gantenerumab program, we pivoted to use the NIH grant to support a decentralized trial comparing different models for returning APOE and ptau217

results. In May 2012, we launched a web-based Alzheimer's Prevention Registry (2). In November 2015, we launched the GeneMatch, a program of the Alzheimer's Prevention Registry (3).

**Preliminary Data, Experimental Design and Methods:**

To accomplish these overall goals and Aim 1, we will analyze data from the API ADAD trial and prepare manuscripts for submission to journals, as well as continue our efforts to share trial data and samples with the scientific community. For Aim 2, we will work with our Novartis and academic colleagues to analyze data and samples from the Generation Program and to implement a data and sample sharing program. To accomplish Aim 3, we will continue to work with our A4 and Lilly colleagues to develop plans for the longitudinal, observational study of individuals who blood-based biomarker test results make them ineligible to participate in Lilly's planned secondary prevention trial of remternetug, collecting data to inform the design of future primary prevention trials. To accomplish Aim 4, we will continue to work with our A4, Lilly, and UPenn colleagues to design a randomized trial of two different return of results delivery models (self-directed vs. healthcare provider-mediated) to disclose genetic and biomarker results to individuals in the abovementioned observational study as well as some trial participants. To accomplish Aim 5, API leadership will continue conversations with pharma companies regarding other potential prevention trials for ADAD or LOAD. To accomplish Aim 6, we will continue to support API-led registries designed to assist with participant recruitment, including efforts to increase participant diversity and bolster registry infrastructure.

**Proposed One-Year and Long-Term Outcomes:**

See above (Preliminary Data, Experimental Design, Methods).

**Year End Progress Summary:**

**Aim 1**. We have submitted two publications describing the cognitive, clinical, and biomarker results from the API ADAD trial. These manuscripts are currently under review at the New England Journal of Medicine. Trial data (cognitive, clinical, and some imaging data) and biological samples are being made available to researchers at LONI and NCRAD. Banner and GNA submitted a R01 grant to the NIA in June 2023 for the next trial in Colombia. We proposed a two-part clinical trial in 200 cognitively unimpaired and mildly impaired PSEN1 mutation carriers and 40 placebo-treated non-carriers from the Colombian kindred. In Part 1, carriers will receive up to 18 months of a plaque-clearing antibody (PCA) treatment (exemplar: donanemab from Eli Lilly), permitting us to compare the magnitude of Aβ PET and plasma pTau reductions in this ADAD kindred to that observed in trials of the same drug in Aβ+ mildly impaired LOAD patients and cognitively unimpaired older adults. In Part 2, carriers would be randomized to receive 1) continued PCA treatment, 2) an oral gamma secretase modulator (GSM) treatment (exemplar: RG6289 from Roche) with the potential to minimize the re-accumulation of Aβ aggregates in a complementary, potentially less expensive, and more scalable way, 3) combined PCA/GSM treatment, and 4) placebo treatment for 18 months. This seamless, double-blind, placebo-controlled, double-dummy study of a PCA and a GSM in cognitively unimpaired and MCI/mild AD PSEN1 E280A mutation carriers will efficiently address a number of key questions including (1) determining the efficacy of a PCA in reducing brain amyloid levels in ADAD; (2) examining the relative efficacy of combination treatment following PCA treatment versus PCA monotherapy versus GSM monotherapy versus placebo to further lower or maintain low brain amyloid levels as well as on downstream biomarkers; (3) estimate how long placebo-treated mutation carriers remain amyloid negative following PCA-induced amyloid clearance; (4) provide a foundation for understanding the longer term clinical impact of the interventions leveraging the Colombian API Registry; and (5) provide invaluable data and samples for the field. This grant received a favorable score; a notice of grant funding is anticipated by end of September 2024.

**Aim 2.** We published a manuscript describing results from the CAD106 program(4). A manuscript describing data from the CNP520 program is currently under review at Alzheimer's & Dementia. A manuscript describing the data from the APOE disclosure program of Generation Study 1 is being prepared for submission to JAMA Neurology. 52,063 aliquots from Generation Study 1 and 72,194 aliquots from Generation Study 2 are available for request through NCRAD totaling 124,256 aliquots of CSF, serum, plasma, DNA, and RNA. These samples are listed in detail and discoverable to the scientific community through an online catalogue hosted at NCRAD's website. Over 6,000 aliquots are available from the screening cohort which contains APOE4 homozygotes, heterozygotes, and non-carriers. Altogether, samples from over 8,000 unique volunteers are hosted at NCRAD and available for sharing. These samples are also linked at a subject level with comprehensive Generation Study 1 and Generation Study 2 trial data hosted at ADDI and USC LONI providing over 1,000 different data elements. Data recipients can also access 6,000 MRI sequences and 5,000 PET sequences at USC LONI, with plans for ADDI to add neuroimaging soon. All available neuroimaging is also linkable to the subject-level samples at NCRAD. We have been actively sharing data and samples from the Generation Program since September, 2023 and have received 40+ requests for access across all platforms to date.

**Aim 3**. Due to programmatic delays and the need to complete this effort by the end of the parent NIH grant, the goals of this Aim are being accomplished under Aim 4.

**Aim 4.** We have shifted gears and will be conducting the eSMARTER trial separate from Lilly's planned secondary prevention trial of remternetug. All 600 participants (200 APOE4 homozygotes, 200 heterozygotes, 200 noncarriers) will be recruited from our GeneMatch program. During the past year efforts have focused on finalizing the study protocol, ICF, risk disclosure materials, contracting with study vendors and partners. We anticipate enrolling the first participant in July or August 2024. All trial data and samples will be made available to researchers to accomplish the aims of the observational study.

**Aim 5.** We published a perspective piece in Lancet Neurology (5) outlining plans to find and support accessibility to the first effective "secondary prevention therapy" in cognitively unimpaired persons with blood test evidence of Alzheimer's disease within the next 2-3 years; find an even more accessible secondary prevention therapy shortly thereafter; and find and support accessibility to the first effective "primary prevention therapy" in older adults who do not yet have blood test evidence of Alzheimer's disease within 4-5 years. This paper builds upon a paper we published earlier in the year examining the cost-effectiveness of a hypothetical AD screening and prevention treatment program(6). We are working to secure philanthropic funds to support convening stakeholders for an API-led AD Prevention Symposium in Fall 2024, prior to launching the first primary prevention trial. We received philanthropic support from the NOMIS Foundation in anticipation of the pending NIH grant for the next API ADAD Trial described in detail in Aim 1. The NOMIS Funds will be used to support the API Registry in Colombia and related activities. We continue to be viewed as leaders in identifying AD risk and protective factors and leveraging these findings for AD prevention treatments. Notably this year we published a paper on the protective effects associated with APOE3 Christchurch heterozygosity in the ADAD kindred in Colombia (7). Aim 6. The Registry and its GeneMatch program continue to grow, with approximately 380,000 people in the Registry (lower than last year due to our efforts remove accounts for which the associated email address is deactivated or undeliverable) and 112,000 in GeneMatch. The STEP-UP R01 is developing evidence-based messaging to increase participant diversity. The R33 grant is improving registry website infrastructure. During the past year we published papers describing the efforts to increase diversity of Registry members and AD-focused studies and the effects of media consumption on willingness to participate in AD related research(8, 9).

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## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Alzheimer's Prevention Registry and its GeneMatch Program.** Jessica B. Langbaum, PhD, Eric M. Reiman, MD, Alireza Atri, MD, PhD, David Coon, PhD. Banner Alzheimer's Institute; Banner Sun Health Research Institute; Arizona State University; Arizona Alzheimer's Consortium.

**Specific Aims:**

Aim 1: To increase enrollment into the Alzheimer's Prevention Registry and its GeneMatch program, particularly within Arizona.

Aim 2: To increase the number of study opportunities available to Alzheimer's Prevention Registry members and GeneMatch participants, particularly within Arizona, by expanding a pilot test a program to help promote studies led by Arizona ADRC and/or AAC researchers.

Aim 3: To provide initial metrics of success at connecting Alzheimer's Prevention Registry and GeneMatch members with study opportunities, particularly within Arizona.

**Background and Significance:**

The suffering caused by Alzheimer's disease (AD) remains one of the greatest unmet medical needs of our times. Interventions that delay onset even by 1 or 2 years would have a major public health impact(1). Considerable effort, attention and funding has been placed on accelerating efforts to prevent and treat the disease, requiring an unprecedented number of healthy older adults to step forward and participate. Enrollment and retention of participants to fill these trials is considered to be the biggest challenges researchers face. Current processes are generally inefficient, contributing to the expense and duration of trials. In the US, recent reviews show that 85-90% of all studies have delays in recruitment and enrollment(2), with 30% under-enrolling and only 7% of sites enrolling the projected number of participants in their originally stated timelines(3). Delayed or inefficient recruitment has scientific, financial, and ethical consequences(4). Moreover, even when trials do meet their enrollment goals, individuals from diverse populations, particularly Black/African Americans and Hispanics/Latinos, are often underrepresented due to a multitude of reasons including mistrust and insufficient dissemination of information. As the field of AD shifts emphasis from recruiting symptomatic patients for treatment studies toward recruiting cognitively unimpaired healthy adults for prevention trials, it is imperative that we understand how to effectively and efficiently recruit, engage and retain participants, with particular attention to recognizing the needs of underrepresented diverse populations. The Banner Alzheimer's Institute launched the web-based Alzheimer's Prevention Registry (www.endALZnow.org) in 2012 as a mechanism to keep the general public informed about the latest news in Alzheimer's prevention research and notify them as study opportunities become available in their communities. The Registry is intended to be a resource to the entire scientific community, helping researchers quickly and efficiently enroll participants into Alzheimer's prevention related studies(5). In 2015, we launched GeneMatch, a program of the APR. GeneMatch is a novel, trial-independent research enrollment program designed to recruit and refer cognitively healthy adults to AD prevention studies based in part on their APOE test results (NCT02564692)(6).

**Preliminary Data, Experimental Design and Methods:**

To achieve Aim 1, we will work to expand Registry and GeneMatch enrollment in Arizona through community outreach efforts, promotion on social media, and other advertising methods as appropriate. For each strategy/tactic, we will track its success. Concerted efforts will be made to increase the enrollment of individuals from underrepresented populations, particularly of individuals who identify as Hispanic/Latino and Black/African American. To achieve Aim 2, 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 junior investigators or researchers new to the AD field. We will develop 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 and use our recruitment services. To achieve Aim 3, we will provide initial metrics of success at connecting Registry and GeneMatch members with study opportunities, particularly within Arizona. We will track referral and enrollment numbers and time to fill sites' enrollment goals to assess the ability of the recruitment programs to accelerate enrollment.

**Proposed One-Year and Long-Term Outcomes:**
Results from this effort will help demonstrate the effectiveness of the Registry and its GeneMatch program at helping studies meet their enrollment goals. In addition, 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:**
During the funding period we used a mixture of social media advertising (e.g., Facebook) and print advertising in local papers in the greater Phoenix metro area. As of June 2024, approximately 380,000 people are in the Registry. This number is lower than the enrollment report shared when the project was submitted in 2023. For database cleanliness, we regularly remove accounts for which the associated email address is deactivated or undeliverable. Approximately 29,168 of these members reside in Arizona. Most members have provided some additional demographic information, but the actual number varies from question to question. Based those who provided additional demographic information, members are predominantly women (75%), report a family history of dementia (54%) (12% are unsure and 14% prefer not to answer) and self-report not having a diagnosis of cognitive impairment (94%). The Registry email newsletters are well-received, with an average open rate of 33%, and unique click rate of 8.6% 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 35.8% and unique click rate of 4.6%.

As of March 2024, the Registry has helped 203 studies with their recruitment needs. The Registry is currently assisting with recruitment for 41 studies, including 17 Arizona-based studies. As of March 2024, nearly 112,000 participants have joined GeneMatch. GeneMatch participants are predominately woman (70%), have a mean age of 69 years. As of March 2024, GeneMatch has helped recruit for 24 studies, including 10 studies led by Arizona investigators with several other being multisite studies with AAC partner institutions serving as performance sites. Since July 2023 (FY 2024 funding), we had 7 Arizona ADRC / AAC researchers / studies submit requests for low to no-cost assistance with their participant recruitment needs. Together the Registry and GeneMatch have referred/invited 6,543 potential participants to Arizona-based studies during, the July 1, 2023-June 30, 2024 funding period.

We continue to collect data under our R01 grant from the NIA (R01AG063954; "Establishing the science behind Alzheimer's recruitment registries: opportunities for increasing diversity and accelerating enrollment into trials"). During the funding period, we published findings from a national survey of 1501 adults ages 50-90, oversampling for Black and Hispanic/Latino respondents, assessing intention to join a generic "brain health" registry and a registry that required specific tasks (e.g., giving a sample of DNA) (7). We reported that intention to join a registry was low, and lower than intention to join a registry requiring specific tasks. Differences in

intention were primary between White and Black women. The results indicate uncertainty about what a registry is, its purpose, and/or the concept of "brain health." We are building upon these results, using the Reasoned Action Approach (RAA) to develop and test evidence-based outreach messages describing a registry to increase diversity of enrollees. Results from these efforts will be published during the next funding period. We also published data from a two-wave national panel of US adults ages 50 and older (n = 1240) to examine the mechanism through which exposure to source-specific news outlets affected willingness to participate in medical research for specific conditions/diseases such as COVID-19 and Alzheimer's. we found support for a spillover hypothesis such that exposure to news sources and attention to COVID-19 issues on those sources were related to willingness to participate in both COVID-19 and AD research, despite a lack of AD news coverage. Furthermore, these relationships worked indirectly through attitudes towards science and COVID-19 misperceptions, with statistically significant indirect effects of political party, education, and other demographics (8).

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## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Returning Results to Research Participants**. Jessica B. Langbaum, 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; University of Arizona; Translational Genomics Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

**Specific Aims:**

Aim 1: To review the literature and available resources to develop draft principles and guidelines for returning research results specific to the Arizona ADRC and its affiliated studies (e.g., Arizona APOE Study).

Aim 2: To partner with other ADRCs to survey return of results practices taking place at centers nationally to inform and refine the principles and guidelines developed in Aim 1.

Aim 3: To develop a pilot study to inform return of results in the Arizona ADRC and its affiliated studies in preparation for the Center's renewal grant application 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 21st Century Cures Act and its associated regulations includes provisions to increase the types of electronic health information that must be easily, immediately, and electronically available to patients. The field must prepare for results of clinically ordered AD-related tests to be released electronically and quickly to patients. 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 obtained from research laboratories (as opposed to CLIA certified laboratories) (2).

**Preliminary Data:**

There is growing interest and demand to return individual research results to participants (1, 2). Indeed, 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. Several research studies have examined the psychological, emotional, cognitive harm effects following disclosure of AD biomarker and/or genetic risk results disclosure (3-6). As part of the API Generation Program, we developed processes for returning APOE and brain amyloid results to participants and assessed the shorter- and longer-term psychological and emotional impact, up to 12-months following disclosure (10). Interim data from 523 participants (163 APOE4 homozygotes, 181 heterozygotes, 179 noncarriers) who underwent first time genetic disclosure as part of screening for the API Generation Study 1 found that there was a slight increase in state anxiety in APOE4 homozygotes in the 2-7 days following disclosure that dissipated by the 6-week follow-up. Disease-specific distress does increase immediately following disclosure (2-7 days after disclosure) among APOE4 homozygotes that declines at the 6 week and 6-month follow-up visits. Measures of depression do not appear to change following disclosure. As part of this effort, we conducted CONNECT 4 APOE, a multi-site, randomized study to evaluate the relative advantages of real-time videoconferencing (RTVC) over telephone for disclosure of APOE results. In the planned interim analysis, 410 participants had been randomized (201 to RTVC, 209 to phone disclosure). Mean participant age was 67 years, 64% are female, 93% White, and >99% have a family history of dementia. 124 (31%) are APOE4 homozygotes and 157 (39%) are heterozygotes. Participant characteristics and test results did not differ significantly between arms. In this early planned analysis, there were no statistically significant differences in change in any measured outcomes from baseline to 2-7 days or 6 weeks post-disclosure. Those in the telephone arm reported less increase in disease-specific distress, although this was not statistically significant. Satisfaction with services was slightly higher in the telephone disclosure arm post-disclosure (0.8 higher in telephone arm, p=0.07). We will analyze the complete Generation Study risk disclosure dataset along with the CONNECT 4 APOE trial dataset in the coming months to inform return of results within the Arizona ADRC and its affiliated studies.

**Experimental Design and Methods:**

To achieve Aim 1, we will conduct a literature review and review available resources for return of results. This may include speaking with ADRD and non-ADRD researchers and clinicians inside Arizona and outside of Arizona to understand return of results in other disease areas. This information will be compiled and used to develop draft principles and guidelines for returning results to specific Arizona ADRC and affiliated studies. To achieve Aim 2, we will partner with leaders from other ADRCs (e.g., UC Irvine, University of Pennsylvania, University of Wisconsin) to develop a survey to understand how other ADRCs are returning results (or planning on returning results). The results from this study may help to inform and refine the principles and guidelines developed in Aim 1. To achieve Aim 3, we will work with leaders from other ADRCs to develop and potentially implement a pilot study on return of results. This data will help guide planning for our Center's renewal application 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 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:**

To achieve Aim 1 and Aim 2, we spoke with subject matter experts at other ADRCs, reviewed guidance from NACC, the literature, and resources from other ADRCs to develop draft principles and guidelines for returning research results specific to the Arizona ADRC and its affiliated studies (e.g., Arizona APOE Study). Notably during this funding period, leaders from the Banner-led API program made substantial progress in preparing to begin enrollment into their NIA-grant funded "Evaluation of Self-Mediated Alternatives for Risk Testing Education and Return of Results" (eSMARTER) Trial. eSMARTER builds off the API Generation Program that that examined the safety and effectiveness of disclosing APOE and brain amyloid results via telemedicine to cognitively unimpaired adults(11). eSMARTER is the next step, evaluating self-directed scalable approaches for communicating AD genetic and biomarker test results. eSMARTER is a decentralized, randomized, non-inferiority trial that is (1) evaluating whether disclosure of AD test results (APOE, blood-based biomarker) to participants by an eHealth platform [either self-directed web-portal (ADWebPortal) or chatbot (ADChatbot)] provides equal non-inferior knowledge, satisfaction, behavioral, and affective outcomes compared to videoconference telehealth disclosure with healthcare provider, (2) characterizing the impact of learning AD test results on the participant, with several other additional exploratory objectives. If the self-directed arm is non-inferior to the healthcare provider arm, we can further develop and deploy these scalable methods for communicating AD gene and biomarker results to participants in our ADRC and affiliated studies.

For the ADRC, as a team we determined it was appropriate to return cognitive/clinical and MRI brain imaging results to participants as a starting point. We noted that amyloid and tau PET are only collected in a subset of participants; no visual read is done for the amyloid PET scans, and there is little-to-no precedent for disclosing tau PET scans. Moreover, the leadership team wanted to leverage "self-directed" return of results materials for disclosing PET results that aren't yet available but will be in late-2025 after the completion of the API led eSMARTER trial. As such, while we aspire to eventually return amyloid PET results to participants, we determined it was premature to do so at this stage, though noted this may change in 2024-2025 with support from the CLARiTI study and data/resources from eSMARTER. We noted that APOE genetic testing and other blood-based biomarker tests (e.g., ptau217), at least for the ADRC these are batch tested / analyzed at NCRAD, complicating the operationalization of returning these results to participants. For now, the leadership team has elected to hold off returning APOE or blood-based biomarker results to participants and will revisit once resources and data from eSMARTER are available.

For the Arizona APOE Study, an affiliated study of the ADRC, we have begun preparatory work to return APOE and amyloid PET results to participants once enrollment is complete or near complete. We will work with the UPenn Telegenetics team to return results to participants using standard videoconference telehealth disclosure. A protocol for returning results will be finalized in the coming months.

To achieve Aim 3, we developed and received IRB approval for letters that will be mailed to participants enrolled at Banner Sun Health Research Institute (BSHRI) ADRC Clinical Core and Brain and Body Donation Program (BBDP) as a pilot program before rolling out to other ADRCs. The letters inform the participant of whether their memory and thinking tests determined that they have no cognitive impairment or whether their results are consistent with impairment (e.g., MCI or dementia). We developed and received IRB for another letter that shares MRI results that may be of clinical significance. Over the next year we will track whether participants reach out to the site to ask questions about the letters and the volume of inquiries. This data will inform the rollout to other ADRCs as we prepare for the Center's renewal grant application in 2025.

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## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**AI-Based Memory Problem Navigator.** Ganesh Gopalakrishna, MD, Lori Nisson, LCSW, Pierre N. Tariot, MD, Alireza Atri, MD, PhD, Allan Anderson, MD, Eric M. Reiman, MD. Banner Alzheimer's Institute; Banner Sun Health Research Institute; Banner Alzheimer's Institute; University of Arizona; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

**Specific Aims:**

The specific aim of this project is to curate a list of questions and most accurate responses that commonly arise as one encounters cognitive impairment, either themselves or by taking care of someone with possible symptoms. The project will seek input from key stakeholders both internally and externally in the community, to obtain key insights and formulate this valuable resource, which can be subsequently made valuable widely leveraging the capability of AI.

**Background and Significance:**

There is a woefully inadequate standard of care for cognitive impaired patients and family caregivers. Banner Alzheimer's Institute (BAI) and Banner Sun Health Research Institute have introduced a care model that aims to address both the medical and non-medical needs of cognitively impaired patients and family caregivers impacted by Alzheimer's disease and related diseases (AD/ADRD), and it has been seeking to extend its approach to those in the primary care setting and those outside our health system. Much of this work depends on institutional and philanthropic resources, limiting its potential scalability to meet the needs of the numerous patients and families in need, and community at large. With the advent of generative artificial intelligence algorithms, we see the opportunity to develop a virtual navigator to address questions of patients, families and providers in real time in cost-effective, equitable and scalable ways. We have sought to begin by identifying common questions that patients and families would ask and engaging technology experts to provide the foundation for the development of an AI-based memory navigator map. Eventually, we would like to build on structured questions to train the algorithm to respond to persons for these and other questions, raised that persons would like to raise in a non-structured fashion and to implement a review and quality-assurance process to ensure the responses are helpful and appropriate while the algorithm continues to be trained.

**Preliminary Data, Experimental Design and Methods:**

We have generated a preliminary list of 200 questions, which will be modified further. We have also generated numerous newsletters, books, and other materials, not yet readily available through the internet to help patients and family caregivers address a wide range of medical and non-medical needs. This information, information from the internet, and other information we will find, will help provide the content used to provide a highly scalable and customizable Open AI-based conversational response to frequent questions from patients with dementia and their caregivers. We have reached out to potential partners, who are leaders in the use of Open AI's GPT Chatbot-4 (GPT4).

**Proposed One-Year and Long-Term Outcomes:**

At the end of year one, we will incorporate input from our internal and external memory problem content and Open AI stakeholders to formulate and categorize up to 300 questions that would address common concerns of PLWD or their caregivers, do so in ways that can optimize an AI-response to questions that are posed in a wide range of ways.

We will ultimately develop the AI-based memory problem navigator, review it for content, and make it widely available to patients, families, and professional caregivers in ways that will help them to better identify the families' medical and non-medical needs.

**Year End Progress Summary:**

The team was able to accomplish the goals set at the beginning of the project as identified in the initial proposal. It was successful in engaging all stakeholders. The project is the first step in establishing a pathway to create an AI driven app supporting caregivers.

Our progress during Q1-Q2 was slower than expected due to delays with receiving IRB exemption for the study. Upon receiving regulatory approvals, we were able to complete our planned activities in a shortened amount of time. We additionally encountered institutional challenges with respect to providing compensation for caregivers/patients who volunteered to take part in the focus groups. Identifying a mechanism to make this possible conveniently was challenging and required efforts from our sponsored projects, finance, procurement and compliance offices to help resolve. Challenges aside, we completed the following accomplishments during the one year period:

• Developed 150-200 commonly asked questions a person, family caregiver or community member might pose to an AI program to access an accurate, on-demand answer.
• Organized questions into topic categories including:
1. Normal aging
2. Alzheimer's dementia Basics
3. Getting a Diagnosis
4. Medical Management Strategies
5. Non-medical Management Strategies
6. Communication and Behavioral Challenges
7. Medical Legal issues in dementia
8. Caregiver support
9. Disease prevention
10. Clinical Trials
• Conducted a focus group of Banner experts to identify relevant themes, additional questions and topics of interest. This helped identify some redundant questions and multiple new questions that was incorporated into the final set.
• Conducted three focus groups among PLWD, caregivers, and key community stakeholders in dementia care to identify relevant themes, additional questions and topics of interest.
• Consulted with AI experts to discuss optimal opportunities to organize questions and leverage the large existing pool of BAI expert-developed educational curriculum in a variety of categories.
• Engaged in conversations with Tap Root Ella, one of the vendors who has similar interests in the space of creating AI driven solutions for patients with dementia. This project establishes the content which will support one of the key interventions in the app which is the desired final product.
• Developed and submitted our new proposal for 2024-2025 to support our continued engagement with stakeholders, AI experts and vendors to further refine, test and implement the virtual application.

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Enhancements to a Centralized Data Management System for the Arizona Alzheimer's Disease Research Center (ADRC), Brain and Body Donation Program (BBDP), and APOE Biomarker Core**. Don Saner, Ricardo Amador, Eric M. Reiman, MD, Robert Bauer, Dave Parizek, BS, and colleagues from each of the participating sites: Banner Alzheimer's Institute; University of Arizona; Arizona State University; Mayo Clinic Arizona; Banner Sun Health Research Institute; Translational Genomics Research Institute; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

**Specific Aims:**

1. Deploy existing ad-hoc report to aactools.org which will enable automated emails to Core Leaders with these data points: 1) When a visit has occurred, 2) When data are uploaded (NACC) and 3) When data are finalized in NACC.

2. Deploy DCC report being piloted at BSHRI to standardize formatting and reduce manual effort and roll out scheduling system to other sites.

3. Continue to upload data to NACC in a timely manner; work with BSHRI to get legacy UDS data up to NACC; upload imaging data to Standardized Centralized Alzheimer's & Related Dementias Neuroimaging (SCAN) including legacy imaging sessions.

4. In anticipation of onboarding a Vendor Supported Biospecimen Management System (VSBMS), we will begin consolidating data on our current catalog of biospecimens.

**Background and Significance:**

The Arizona Alzheimer's Consortium supports three longitudinal research programs that are internationally recognized for their productivity, impact, and value to researchers inside and outside of Arizona in the scientific fight against Alzheimer's Disease (AD), Parkinson's Disease (PD), and related disorders, and the study of normal brain aging. These programs include common data elements, are administered through separate data management programs, and could provide even greater value under a common data management program that is optimized to fulfill the programs' common and complementary research goals.

1) With support from the National Institute on Aging (NIA), the Arizona ADRC Clinical Core is the nation's first NIA-sponsored AD Center with multiple clinical core sites (including those at Mayo Clinic Arizona, BSHRI, UA, BNI, and BAI). The Core provides annual assessments in ~500 research participants with AD, related disorders, and cognitively unimpaired older adults; it includes individuals who are enrolled in BSHRI's BBDP, cognitively unimpaired individuals with two, one, and no copies of the APOE4 allele (the major genetic risk factor for AD), members from Arizona's understudied Latino and Native Indian communities, and other clinically affected and unaffected research participants; and it provides a shared resource of participants and data for researchers to generate new findings, publications, and grants.

2) The BBDP includes >800 annually assessed research participants from the ADRC, the National Institute for Neurological Disorders (NINDS)-supported National Brain and Tissue Resource for PD (NBTR-PD), and other longitudinally assessments from older adults who consent to brain donation after they die, neuropathological data, and exceptionally high quality brain and body tissues from >1,500 expired BBDP participants. It has been the world's leading resource of neuropathology data and brain and other body tissue samples for AD, PD, and other

neurodegenerative disease researchers around the world, has contributed to hundreds of research publications and grants, and continues to make major contributions to the study of AD, PD, related disorders, and brain aging.

3) With support from the NIA, the state of Arizona, Mayo Clinic and BAI, the Arizona APOE Biomarker Core provides a longitudinal cohort of research participants and data with two, one, and no copies of the APOE4 gene, reflecting three levels of genetic risk for AD, including a sub-set of subjects with extensive brain imaging and other biomarker data. This program has made pioneering contributions to the conceptualization of "preclinical AD," established a foundation for the Alzheimer's Prevention Initiative (API) and the accelerated evaluation of prevention therapies, and includes an invaluable resource of data and samples to help researchers detect and track the earliest biomarker and cognitive changes associated with AD, contribute to the understanding of genetic and non-genetic risk factors, develop data analysis techniques with improved power to detect and track AD and evaluate promising but unproven AD prevention therapies. Consortium researchers lead other valuable longitudinal research programs, which despite fewer common data elements, may benefit from either a shared data management program and/or mechanisms to find other relevant data in the future.

**Preliminary Data:**

With an increased focus on leveraging Blood Based Biomarkers for diagnostic purposes we continue to collect biospecimens that are banked at the National Centralized Repository for Alzheimer's Disease (NCRAD) as well as banking them locally. Our current methods of tracking samples are based in spreadsheets, REDCap and MSACCESS which we anticipate will not be able to accommodate the increased volume of samples, so we are seeking a VSBMS. To date, we have met with the UA biobank and the NCRAD biobank to help inform the requirements for a Request for Proposals (RFP). We identified nine potential vendors of which five have expressed interest in the RFP process. Once the selection process is completed, we will need to work with the selected vendor to transfer data on our existing catalog of biospecimens into the new system.

During the past year we have continued to refine our reports to capture visits shortly after the completion and prior to the completion of REDCap data entry which has helped support our enrollment led by our ORE and Clinical Cores to gain insights into our projected enrollment once all packets have been finalized at the National Alzheimer's Disease Center (NACC). We extended Site specific reports to include enrollment based on header information, working and finalized with the ability to download NACC PTIDS for each category. Additional data points were added to show participants that were overdue for a visit as well as those that should be scheduled for a new visit. Information on milestones and cases presented at DCC meeting is now also available. We again presented a poster at our annual Arizona Alzheimer's Consortium Conference held at the Arizona State University in September 2022 highlighting the tools that are available to our consortium members and data that can be requested either from our local consortium or through NACC. During the current funding period we assisted seven investigators in requesting NACC data and formatting/filtering the data to get it in an analytic friendly format which may result in publications and/or grants.

**Experimental Designs and Methods:**

We have engaged with Banner IT's Vendor Management team and domain experts to author an RFP and have identified five potential venders interested in submitting proposals. Non disclosure agreements are currently being negotiated with the five venders. Once these have been signed we will send our RFP out and then schedule product demonstrations including those directly

working with our biobanking efforts. Once a vendor has been selected we will engage with the appropriate teams within Banner to bring the solution online. The Data Management Core will work with the vendor to translate our existing catalog of biospecimens into the Vendor's solution.

While we have improved reporting from visits prior to packet completion utilizing MS PowerBi, our ad-hoc reporting tool, we will incorporate this report into our online portal at aactools.org with the ability to subscribe to have it emailed on a monthly basis. We are piloting a Diagnostic Consensus Conference (DCC) report which generates the excel spreadsheet used to present cases at the DCC and are tedious to generate by hand. We are piloting this with BSHRI who has adopted REDCap for a subset of their Clinical Core Participants and once we have this fully functional we intend to roll it our to other sites within our Arizona Consortium. We also piloted a scheduling system in REDCap with BSHRI that we will role out to other sites with any modifications needed to accommodate site specific workflows. We have continued to better understand the Brain and Body Program's MSSQL database and have created the first draft of an Entity Relationship Diagram (ERD) which we will continue to refine and will be critical for the success of a VSBMS. We will continue to upload imaging sessions from our Clinical Core to the SCAN and from our affiliated programs one year after the imaging sessions. We continue to work with BSHRI to get legacy UDS data transmitted to NACC with a priority placed on participants with Imaging and/or Biospecimens. Also, as in previous years we presented a poster at the fall consortium conference to continue to drive awareness of the tools we have locally and what we can assist with in terms of national repositories of data.

**Proposed One-Year and Long-Term Outcomes:**

Moving the early enrollment report to our aactools.org site will enable Core leaders to receive automated monthly reports by email instead of waiting for our monthly ORE meeting for updates. Being able generate DCC reports through our aactools.org site will save sites significant time by automatically generating the reports from REDCap data for the DCC meetings. Implementing our scheduling system to sites beyond BSHRI will create standardization across sites and enable new reports from these data that may give new insights. By continuing to document and understand data in the BSHRI's MSSQL system, we can assist in migrating data to a new VSBMS. By uploading current and legacy SCAN and UDS data we are contributing to a large standardized data set which will enable research within our consortium with expanded access to other sites submitting to SCAN and NACC.

**Year-End Progress Summary:**

1) Participant Tracking Reports: We deployed two reports: one for the Alzheimer's Disease Resource Center and another for the Arizona APOE Biomarker Core. These reports track participants at three time points:

- When a participant visit occurs
- When participant data is uploaded to the National Alzheimer's Coordinating Center (NACC)
- When participant data is finalized in the NACC

The updated reports include race and ethnicity, providing core leaders with a better understanding of the eventual cohort size for both programs by demographic breakdown. These reports are emailed to core leaders monthly.

2) Diagnostic Consensus Conference Report: We are finalizing a report that contains a longitudinal record of participant history along with their current neurocognitive assessments. This report will be used by conference participants to reach a consensus on each participant's current diagnosis. Automating this report will significantly save staff time.

3) Data Uploads: We have continued timely uploads to the NACC. This includes legacy data from Banner Sun Health Research Institute that had not been previously uploaded and passed the NACC's extensive data checks. A total of 77 uploads have been completed, and 66 are in progress. Additionally, we have uploaded legacy imaging sessions to the Standardized Centralized Alzheimer's & Related Dementias Neuroimaging (SCAN) database.

4) Vendor Supported Biospecimen Management System: Our first meeting with a vendor responding to our Request for Proposals is scheduled for June 7th. This will be a technical demonstration to assess the compatibility of their hosted solution with our policies and procedures.

# BANNER ALZHEIMER'S INSTITUTE - TUCSON
# PROJECT PROGRESS REPORTS

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Hispanic Outreach, Recruitment, and Retention Program.** Steven Z. Rapcsak, MD, Jeremy Pruzin, MD, Marisa Menchola, PhD. Banner Alzheimer's Institute, Tucson; Banner Alzheimer's Institute, Phoenix; Midwestern University; Arizona Alzheimer's Consortium.

**Background and Significance:**

Hispanic/Latino adults are disproportionately affected by Alzheimer's disease (AD) and the number of impacted individuals is expected to increase exponentially over the coming years. Despite the higher disease burden, Hispanic/Latinos are an underrepresented group in biomedical research on AD. Thus, there is an urgent need to increase the participation of Hispanic/Latino individuals in research studies and clinical trials. Banner Alzheimer's Institute in Tucson (BAI-T) is located in a region with a Hispanic/Latino population of 45%, and is therefore uniquely positioned to advance this goal. This project is designed using a community-based approach to increase research participant engagement and AD study enrollment for this underrepresented group and complements enrollment efforts for the Arizona ADRC Outreach and Clinical Cores.

**Specific Aims:**

Aim 1: To develop strategic alliances and build coalitions with organizations that have established networks in the Hispanic/Latino community and to collaborate with community partners on service-related outreach events throughout the Tucson area.
Aim 2: To use innovative approaches to effectively engage with Hispanic/Latino populations, raise AD awareness, and share information about the importance of early clinical diagnosis, access to state-of-the-art treatment, and research participation, with the goal of increasing enrollment of Hispanic/Latinos in AD research studies and clinical trials.
Aim 3: To develop and offer culturally tailored educational content on reducing risk of dementia, AD, and the importance of clinical trial participation.

**Year End Progress Summary**:

BAI-T has collaborated with a variety of community partners on multiple outreach efforts in the Hispanic/Latino community, including:

- Three community education programs with bilingual presentations on "Reducing Risk of Dementia & The Importance of Alzheimer's Disease Research".
- Four public events and two health fairs providing AD and brain health educational materials in English and Spanish.
- Two senior center social engagements and two Medicare clinic visits in largely Hispanic/Latino neighborhoods to provide AD resources to both patients and staff.

Additionally, we have provided two professional educational programs, both virtual and in-person, on the impact of AD in the Hispanic/Latino community. We have developed several pieces of brain health literature in English and Spanish, and have distributed over 50 toolkits on topics such as cognitive aging, early recognition and diagnosis of AD, and caring for someone with AD. Currently, we are working on a 3-part video series that features a Hispanic/Latino family impacted by AD in multiple family members. Each video covers a different topic, and these will be distributed on broadcast and social media. These efforts have resulted in the enrollment of five Hispanic/Latino participants into the Arizona ADRC study.

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Characterizing Empirically Derived Cognitive Subtypes in the National Alzheimer's Coordinating Center**. Emily C. Edmonds, PhD, Steven Z. Rapcsak, MD, Shannon Lindemer, MS, Kelsey Thomas, PhD, Lisa Delano-Wood, PhD, Mark Bondi, PhD, David Salmon, PhD. Banner Alzheimer's Institute, Tucson; University of Arizona; University of California, San Diego; Veterans Affairs, San Diego Healthcare System; Arizona Alzheimer's Consortium.

**Background and Significance:**

Accurate diagnosis of early phases of Alzheimer's disease (AD) is critical for identifying individuals who are at risk for progression to dementia for the purpose of early intervention or enrollment in clinical trials aimed at modifying the disease process. Previous work has shown conventional methods for classifying mild cognitive impairment (MCI) are prone to diagnostic errors and do not capture heterogeneity within MCI samples. Conventional methods also do not identify subgroups of cognitively normal (CN) individuals. Alternative approaches that use sensitive neuropsychological measures and data-driven methods to classify MCI and CN can improve diagnosis and produce groups with stronger associations between cognition, biomarkers of AD, and risk for dementia compared to conventional methods.

**Specific Aims:**

Aim 1. To examine differences in A/T/N classification using AD biomarkers of amyloid (A) and tau (T) from cerebrospinal fluid (CSF) and PET scans, as well as neuroimaging biomarkers of neurodegeneration (N) in our empirically-derived cognitive subgroups. Aim 2. To examine structural neuroimaging biomarkers in our empirically-derived cognitive subgroups. Aim 3. To examine neuropathology in a subset of our empirically-derived cognitive subgroups.

**Preliminary Data:**

Cluster analysis was applied to baseline neuropsychological test data from 26,255 NACC (National Alzheimer's Coordinating Center) participants age 50+ without dementia. Tests assessed learning/memory, attention/working memory, attention/executive functioning, and language. Results revealed 5 cognitive subgroups:

1. Optimal CN (oCN) with above-average to average cognition in all domains
2. Typical CN (tCN) with average cognition across domains
3. Amnestic MCI (aMCI) with isolated low memory performance
4. Mixed MCI-Mild (mMCI-Mild) with low performance across domains
5. Mixed MCI-Severe (mMCI-Severe) with more severe multi-domain impairment

Survival analysis showed that rates of progression to dementia differed significantly across the five groups (oCN < tCN < aMCI < mMCI-mild < mMCI-severe). Comparison of our subgroups to NACC's consensus diagnoses showed that our data-driven methods provided more nuanced, precise predictions of risk.

**Experimental Design and Methods:**

We will characterize our NACC subgroups on biomarkers and neuropathology. Aim 1: For A/T/N classifications, positivity for amyloid (A) and tau (T) will be determined via CSF biomarkers or brain imaging. Positivity for neurodegeneration (N) will be determined via neuroimaging biomarkers of neurodegeneration (hippocampal atrophy; FDG-PET pattern of AD), or CSF biomarkers. Aim 2: Groups will be compared on hippocampal volume and cortical thickness within the frontal, temporal, and parietal lobes. Aim 3: Groups will be compared on Braak stage for

neurofibrillary degeneration and on other pathologies (vascular, hippocampal sclerosis, Lewy body disease, frontotemporal lobar degeneration).

**Year End Progress Summary:**

We made significant progress on this project, as reflected by the milestones below:

1. We published a study where we described identification of cognitive sub-groups in MCI and CN subjects using baseline neuropsychological test data from 26,255 NACC participants:
Edmonds EC, Thomas KR, Rapcsak SZ, et al. Data-driven classification of cognitively normal and mild cognitive impairment subtypes predicts progression in the NACC dataset. Alzheimers Dement. Published online April 4, 2024. doi:10.1002/alz.13793

2. We presented results from the study above at the 52nd annual meeting of the International Neuropsychological Society in New York City, NY in February 2024, and at the Arizona Alzheimer's Consortium annual retreat in Phoenix, AZ in March 2024.

3. We conducted analysis of AD-specific biomarkers of amyloid in the MCI and CN neuropsychological subgroups. Analyses of amyloid PET in a subset of the NACC sample (n=937) showed that amyloid positivity increases across the cognitive subgroups (oCN = tCN < aMCI = mMCI-Mild < mMCI-Severe). We also found significant differences in amyloid PET positivity between the subgroups of "normal cognition" within a subset of the NACC sample (n=410).

4. We established a collaboration with Dr's Yi Su and Hillary Protas of the ADRC Biomarker Core in order to examine neuroimaging biomarkers in our empirically-derived cognitive subgroups (Aim 2). They will provide their expertise in conducting analyses of structural MRI (magnetic resonance imaging) biomarkers with the NACC subgroups.

5. We performed a systematic review of subtle cognitive decline (SCD) literature in collaboration with a researcher at the University of California San Diego. Results showed multiple methods for defining SCD. Across multiple methods, there was consistent evidence that objective SCD can be detected prior to MCI and is associated with ADRD biomarkers, neuroimaging results, and faster rates of progression to MCI/dementia. Results of the review have implications for clinical trial recruitment and for the ethics and potential use of objective SCD criteria in clinical practice. An abstract with these findings was submitted for the upcoming Alzheimer's Association International Conference (AAIC). The manuscript was submitted for publication in May 2024.

6. Dr. Emily Edmonds received a subaward for a funded NIH RF1 grant, entitled, "Heterogeneity of subtle cognitive decline phenotypes in community-dwelling older adults" (NIH/NIA 1 RF1 AG082726-01 [9/1/2023-8/31/2028]; PI: Kelsey Thomas, PhD). This project will use a data-driven approach to examine the heterogeneity of cognitive profiles in older adults from the Atherosclerosis Risk in Communities (ARIC) Study and Baltimore Longitudinal Study of Aging (BLSA) cohorts and determine how these unique cognitive profiles relate to ADRD biomarker profiles, vascular risks, and physical activity as well as future rates of progression to MCI/dementia. The project is a collaboration between researchers at the University of California San Diego, Banner Alzheimer's Institute, the University of North Carolina, and Johns Hopkins University.

7. Dr. Edmonds and co-investigator Dr. Rapcsak have a planned R01 grant submission for July 2024 in collaboration with Dr. Matthew Grilli and other researchers at the University of Arizona. The proposed project, which is aimed to examine the potential value of assessing semantic memory to identify early stages of AD pathology, will employ empirical methods of identifying SCD and MCI in older adults.

# BANNER SUN HEALTH RESEARCH INSTITUTE
# PROJECT PROGRESS REPORTS

# ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Augmenting Under-Represented Group Outreach, Recruitment, Enrollment and Retention in the Arizona Alzheimer's Disease Research Center Clinical Core Cohort.** Alireza Atri, MD, PhD, David Weidman, MD, Steven Rapcsak, MD, Meredith Wicklund, MD, Jessica Langbaum, PhD, Eric Reiman, MD, David Coon, PhD. Banner Sun Health Research Institute; Banner Alzheimer's Institute, Phoenix; Banner Alzheimer's Institute, Tucson; University of Arizona; Mayo Clinic Arizona; University of Arizona, College of Medicine-Phoenix; Arizona State University; Arizona Alzheimer's Consortium.

**Specific Aims**:

1) To augment and enhance Under-Represented Group (URG), including but not limited to Hispanic-Latino and Native American, outreach, recruitment, enrollment and retention in the Arizona Alzheimer's Disease Research Center (AZ ADRC) Clinical Core Cohort by developing, coordinating and supplementing efforts within and between Banner Sun Health Research Institute (BSHRI), Banner Alzheimer's Institute – Phoenix (BAI-P), Banner Alzheimer's Institute – Tucson (BAI-T), and Mayo Clinic Arizona (Mayo AZ) sites.
2) To enhance and forge strategic alliances with organizations that have established networks in URG communities to amplify the reach of the Arizona Alzheimer's Consortium and AZ ADRC.
3) To achieve at least 25 additional new enrollments of URG participants in the AZ ADRC clinical core cohort.

**Background and Significance:**

The prevalence and impact of Alzheimer's disease (AD) and related disorders (ADRD) are expected to dramatically increase in the coming decades. Older adults from Under Represented Groups (URGs), including Hispanic/Latinos, Native Americans and Blacks, are disproportionately more likely than White older adults to develop and be impacted by AD/ADRD. Furthermore, the number of URG, including Hispanic and Native American, older adults suffering from AD/ADRD is expected to drastically increase over the coming decades. Multiple biological and social factors likely contribute to the higher risk and prevalence of AD in URGs compared to White non-Hispanics. These factors include potential differences in genetic susceptibility and biomarker profiles, medical comorbidities that increase risk of cognitive decline and dementia (e.g. hypertension, diabetes, cardiovascular and cerebrovascular diseases, stroke), as well as socioeconomic disparities, lower education, and limited access and utilization of healthcare resources. However, URGs remain under-represented in AD/ADRD-related biomedical, observational and biomarker research and clinical trials, including in important national cohort studies such as the NIA-funded Alzheimer's Disease Research Center (ADRC) National Alzheimer's Coordinating Center Uniform Data Set (NACC UDS) longitudinal cohort. An urgent need remains to increase awareness, participation and retention of URGs in AD/ADRD-related observational and biomarker research studies and clinical trials; and to improve our understanding of disease mechanisms and clinical and biomarker trajectories related to URG populations.

From 2005 to the present, ADRCs have been contributing data to the NACC UDS, using a prospective, standardized, and longitudinal clinical evaluation of participants in the National Institute on Aging's ADRC Program. In each participant's annual ADRC clinical core cohort UDS visit, 16 data-collection forms are assessed and completed by the clinician, covering topics from subject demographics, to neurological examination findings, to syndromic and etiologic

diagnoses. Many participants in the AZ ADRC clinical core cohort also provide biomarker data by contributing blood samples and/or undergoing studies such as brain MRI or PET scans.

This project aimed to develop, coordinate and supplement efforts within and between ADRC BSHRI, BAI-P, BAI-T, and Mayo Clinic AZ sites to augment and enhance URG, including but not limited to Hispanic-Latino and Native American, outreach, recruitment, enrollment and retention in the AZ ADRC clinical core cohort. The project also aimed to enhance and forge strategic alliances with organizations that have established networks in URG communities to amplify the reach of the Arizona Alzheimer's Consortium and AZ ADRC, and to achieve 25 additional new enrollments of URG participants in the AZ ADRC clinical core cohort between July 1, 2023 and June 30, 2024. Funds from this project are also used in ways that complement, augment and enhance but do not overlap with funding provided by the National Institute on Aging (NIA) for AZ ADRC outreach and clinical core URG enrollment activities and stated goals; or by any other funding agency.

**Preliminary Data:**

The AZ ADRC Clinical Core Cohort, currently early in year-4 of NIA funding, has approximately 610 active participant enrollments finalized or pending enrollment data verification in the national ADRC NACC UDS cohort; and 159 of these participants self-identify as belonging to an URG. The AZ ADRC is committed to increasing URG participant engagement and enrollment and compared to Arizona demographic data there remains room for improvement of URG participation and enrollment in AZ ADRC clinical core cohort. The AZ ADRC has stated goals of enrolling, by year-5 of NIA funding, at least 550 active participants, and at least 175 participants are proposed to be from Hispanic/Latino and Native American URGs.

**Project Information:**

Recent initiatives at BSHRI, BAI-P, BAI-P and Mayo Clinic AZ ADRC sites have made strides to improve URG outreach and enrollment. However, there remains great potential to augment, coordinate, supplement and better leverage efforts within and between sites, and to strengthen relationships with URG organizations and communities to achieve additional URG outreach, recruitment, enrollment and retention in the AZ ADRC clinical core cohort. These efforts include advertising, outreach, engagement and recruitment at BAI-T and Mayo Clinic AZ focused on Hispanic/Latino organizations, communities and individuals; at BAI-P focused on Native American organizations, communities and individuals; and at BSHRI focused on Black/African American organizations, communities and individuals. This project will coordinate, extend and expand these and new efforts by utilizing project funds in meaningful ways that complement, augment and enhance but do not overlap with other funding, including those provided by the NIA AZ ADRC. Project metrics on outreach, recruitment, and engagement activities and contact and enrollment numbers and outcomes will be collected.

**Proposed One-Year and Long-Term Outcomes:**

1) Better coordination and collaboration among and within four sites to expand URG outreach, recruitment, enrollment and retention in the AZ ADRC clinical core cohort
2) Leverage and enhance emerging partnerships and build strategic alliances with organizations that have established networks in URG communities to broaden and strengthen AAC and AZ ADRC reach in URG populations
3) Achieve at least 25 additional new enrollments of URG participants in the AZ ADRC clinical core cohort
4) Contribute to greater diversity, equity, inclusion and increased awareness, participation and retention of URGs in AD/ADRD-related longitudinal observational and biomarker research; and

to improve understanding of disease mechanisms and clinical and biomarker trajectories related to URG populations.

**Year End Progress Summary:**

Outstanding progress was made during the grant funding year (FY2023) from July 1, 2023 through June 30, 2024 (see Table 1 and below) toward achieving the specific aims of this project.

| URG | New Enrollment | MRI scan | PET scan | Plasma |
|---|---|---|---|---|
| Asian | **1** | **0** | **0** | **3** |
| Black or African American | **2** | **0** | **0** | **3** |
| Native American | **14** | **6** | **7** | **11** |
| Native Hawaiian or Pacific Islander | **1** | **0** | **0** | **0** |
| Non-white Hispanic | **2** | **1** | **2** | **2** |
| White Hispanic | **18** | **15** | **10** | **28** |
| Total | **38** | **22** | **19** | **47** |

**Table 1.** AZ ADRC clinical core Under-Represented Group (URG) new participant enrollments and biomarker studies (MRI and PET scans) obtained and plasma samples collected during grant funding report year FY2023 (July 1, 2023 through June 30, 2024).

**Progress toward Specific Aim 1 and One-Year and Long-Term Outcomes 1,2 and 4:**

**Excellent progress was made toward achieving this specific aim and outcomes during the funding year. A strong foundation of** coordination and collaboration between and within the four AZ ADRC sites was further cemented to expand URG outreach, recruitment, enrollment and retention in the clinical core cohort. Further, strategic alliances with organizations that have established networks in URG communities were established and enhanced to amplify the reach of the Arizona Alzheimer's Consortium and AZ ADRC. In addition to the outstanding results (see Table 1) in regards to URG new enrollment and data, and biomarker study and samples collection, 13 collaborative outreach, educational and service events (focusing on brain health, AZ ADRC and AD/ADRD research and study opportunities) targeting, to great extent, URG communities were conducted, including Prayer Assembly COGIC (2 events, 1 predominantly focused on Black/African American persons), Archwood Exchange Marketplace (5 events predominantly focused on Black/African American persons), Outreach West Valley (1 events focused on Black/African American barber shop), City of Phoenix Beuf Senior Center Brain Health Education (1 event), City of Glendale Annual Employee Benefits and Wellness Fair (1 brain health education event), Teague Library Free Comic Day (1 brain health education event), FIBCO Family Services Community Health Fair (1 brain health fair event predominantly focused on Black/African American persons). These events included over 2500 participants (>80% URG); generated 870 direct interactions and provision of outreach information, education or services (including 60 free memory and cognition screenings); and resulted in 25 study enrollments.

**Progress toward Specific Aim 2 and One-Year and Long-Term Outcomes 3:**

Outstanding progress was made toward achieving this specific aim and outcomes during the funding year. As reflected in Table 1, during grant funding report year FY2023 (July 1, 2023 through June 30, 2024), there were 38 URG AZ ADRC clinical core Under-Represented Group (URG) new participant enrollments, 22 MRI and 19 PET scans obtained and 47 plasma samples collected from URG participants.

# ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Development, Validation and Implementation of Cognitive and Clinical Composites for the Arizona Study of Aging and Neurodegenerative Disorders/BBDP**. Alireza Atri, MD, PhD, Briana Auman, PhD, Autumn Arch, Christi Belden, PsyD, Geidy Serrano, PhD, Thomas Beach, PhD, Kewei Chen, PhD, Matt Huentelman, PhD, Michael Malek-Ahmadi, PhD, Jessica Langbaum, PhD. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium; Arizona State University; Banner Alzheimer's Institute; Translational Genomics Research Institute.

**Specific Aims:**

1) 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.

2) 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)

3) 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 Brain and Body Donation Program (BBDP) at Banner Sun Health Research Institute (http://www.brainandbodydonationprogram.org) started in 1987 with brain-only donations and has banked more than 2275 brains and contains a rich and unmatched clinico-pathological dataset that has, in more recent years, been greatly enriched with structural, metabolic (PET) and fluid (cerebrospinal fluid and blood samples) biomarker data from participants. The BBDP is responsible for seminal research findings including clinico-pathological correlations in cognitive aging, Alzheimer's disease (AD) and related disorders (ADRD), and AD/ADRD biomarker validation (including imaging, e.g. amyloid and tau PET, and fluid biomarkers, such as blood-based biomarkers); and has accounted for >500 scientific publications, and hundreds of scientific presentations and grants (recently ranging from 30-60 peer-reviewed impactful publications/year, dozens of presentations at regional, national/international conferences/year, and 40-60 grants/year). The collective academic output of BBDP is described as the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND).

Most BBDP participants are enrolled as cognitively normal volunteers residing in the retirement communities of metropolitan Phoenix, Arizona. Specific recruitment efforts are also directed at participants with AD, Dementia with Lewy Bodies (DLB), Parkinson's disease (PD) and cancer. The median age at death is 83.0 years. 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 by medically licensed pathologists after death.

Prior to 1996, BBDP participants data were abstracted from medical records and participants did not undergo standardized cognitive and neuropsychological assessments. Since 1996, while some assessments or tests have remained constant (e.g. the Mini-Mental Status Exam – MMSE), others have not. These include many specific neuropsychological tests of attention, memory, language, executive functions, and visuospatial cognition; as well as assessments of global

staging (e.g. Functional Assessment Scale, Global Deterioration Scale, Clinical Dementia Rating scale). Since the MMSE is the global brief cognitive test that has available longitudinal data for the majority cases where autopsy data is also available, it has led to it being used as the general proxy for "cognition" (and even global cognitive-functional or dementia staging) when assessing clinico-pathological relationships in BBDP projects. While using the MMSE has allowed for maximizing the number of autopsy cases for which a longitudinal BBDP "cognitive" measure is available, due to MMSE's relatively blunt nature as a brief cognitive screening measure designed to detect dementia-level impairment (that is also insensitive to detect mild cognitive impairment, MCI, and subject cognitive decline/changes, SCD, particularly in more educated participants) has led to insensitivity to explicate clinico-pathological, age-, and disease-specific relationships with global cognition, and more so with specific neuropsychological domains (e.g. attention, memory, language, executive functions, visuospatial cognition).

The advantages of cognitive and clinical composites (e.g. PACC, APCC, iADRS, and ADCOMMS) in cognitive aging and ADRD research are well described and composites are endorsed by the United States Food and Drug Administration (FDA) for pivotal clinical trials (Schneider et al. 2020; Langbaum et al. 2020; Donohue et al. 2014, van Dyck et al. 2022; Tahami Monfared et al. 2022). Development and use of cognitive and clinical composites have explicated clinico-neuropathological/biomarker relationships and accelerated discoveries in multiple clinico-pathological and longitudinal biomarker cohort studies and clinical trials. **Developing, assessing, refining and implementing composites appropriately-suited to the BBDP/AZSAND will substantially increase the ability to maximally harness the power of this important study (e.g. not just relying on MMSE as a relatively insensitive measure of global cognition or clinical stage). It will greatly enhance BBDP/AZ SAND's impact in the coming years not only to explicate neuropath-biomarker-clinical relationships and to advance science, but will also accelerate the pace of developing and implementing effective therapeutic biomarker and therapeutic approaches for research and in the clinic to benefit patients and families affected by AD/ADRD.**

**Experimental Designs and Methods:**

A comprehensive inventory, cataloguing and classification of data and tests, assessments and variables, particularly those related to cognition and neuropsychological domains, activities of daily living (daily function), neuropsychiatric symptoms and behavior, and global and clinical severity and staging, across the multiple and overlapping BBDP/AZ SAND databases is undertaken; and, through an assessment and consensus process, classification of measures into domains is achieved (Aim 1 and 2). There are several commonly used approaches to generate domain-specific composite scores. One is empirically derived and cross-validated, and the other is based on multivariate statistical techniques including principal component analysis (PCA) and other conceptually similar approaches. We use primarily the empirically derived and cross-validated approach via 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). As an alternative, we secondarily evaluate the use of PCA for composite score formation. These composite scores can be domain specific (e.g. where PCA component 1 is memory specific and component 2 executive function specific). Finally, we explore the use of machine learning (ML) approaches especially artificial neural network approach for establishing composite score. For exploratory ML/artificial neural network investigations, the interpretability of the constructed composite score is placed as top priority thus mitigating, as demonstrated in numerous studies, any potential challenges regarding performance and practical applicability of these approaches.

**Year End Progress Summary:**

In this first year of grant funding (FY2023), there was very good progress toward achieving the project aims. We undertook a comprehensive inventory, across multiple and overlapping

BBDP/AZ SAND databases, and catalogued and made assessments and preliminary assignments/classifications of measures into categories and domains for data, tests, assessments and variables, particularly those related to cognition and neuropsychological domains, activities of daily living (daily function), neuropsychiatric symptoms and behavior, and global and clinical severity and staging (AIM 1 and AIM 2). We also explored quantitative approaches, including SEM and ML, to classification and composite development (AIMS 1-3), and assessed neuropathological profiles in BBDP participants with MCI, which resulted in a prestigious oral presentation at the American Academy of Neurology (AAN) annual international conference (Denver, CO, April 2024).

The BBDP databases (as of April 2024) include more than 2,275 brain autopsies, 943 body autopsies, 1687 CSF samples, and 1914 serum samples. Participants with autopsy data and at least one assessment in the data base included data for 1021 participant MMSEs, 1017 participant neurologic exams, 1039 participant neuropsychological exams, and 1100 participant-specific movement exams. Clinicopathologic diagnosis available include 418 cognitively unimpaired controls, 935 with AD, 257 with PD, 171 with DLB, 182 with Vascular Dementia, 82 with Hippocampal Sclerosis, and 54 with FTLD-TDP. BBDP participants also had thousands of plasma and hundreds of CSF samples; and >650 total scans over the past 5 years (PET scans for plaques (amyloid), tangles (tau), synapses (SV2A) and/or structural brain changes (MRI)).
We undertook an extensive assessment, cataloguing (including timeframes/spans) and preliminary classification of the cognitive tests and measures used since the inception of the BBDP/AZSAND and found 88 cognitive tests and summary or global measures and assessments have been utilized over the last 25+ years. We preliminarily 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) (AIM 1 and AIM 2). We also 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) (AIM 3).

We explored and characterized clinical and cognitive/neuropsychological profiles of participant donors who were in the MCI stage when their brain was donated (AIM 3). We performed a preliminary analysis of BBDP/AZSAND cases which was presented at an oral platform presentation at the American Academy of Neurology, AAN, International Conference (Ho A, Choudhury P, Adler CH, Shprecher DR, Mehta, S, Shill HA, Driver-Dunckley E, Belden C, Serrano G, Beach T, Atri A, Tremblay C. Neuropathological Profile of Cases with Mild Cognitive Impairment. American Academy of Neurology (AAN) International Conference, Denver, CO, April 14, 2024). The comparison included participant donors with a final consensus cognitive diagnosis of MCI (n= 128) prior to death to a cohort of cognitively unimpaired donors (n=195). Groups were further divided into amnestic (aMCI) and non-amnestic MCI (naMCI), as well as single and multi-domain impairment. Presence and severity of neuropathology including AD, LB, cerebral white matter rarefaction (CWMR), cerebral amyloid angiopathy (CAA), cerebral infarcts and microinfarcts (cortical and subcortical), TAR DNA-binding protein 43 (TDP-43), and apolipoprotein E (ApoE) status were compared between MCI and cognitively unimpaired cases, as well as MCI subtypes. The preliminary analysis suggests that AD pathology was higher in MCI; Cerebral White Matter Rarefaction (CWMR) is more common when executive functions are impaired; and that vascular brain injury/pathology including subcortical infarcts, CWMR and Cerebral amyloid angiopathy (CAA) appear to be commonly associated with both amnestic MCI and non-amnestic MCI. CWMR and LBs also appear to be more frequent in multidomain aMCI and naMCI, respectively.

# ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Enhancing Clinical and Biological Characterization of The Longevity Cohort Study: Global Staging and Biospecimen Banking.** Alireza Atri, MD, PhD, Christi Belden, PsyD, David W Coon, PhD, Briana Auman, PsyD, Autumn Arch, Geidy Serrano, Thomas Beach, PhD, Kewei Chen, Matt Huentelman, Michael Malek-Ahmadi. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium; Arizona State University; Banner Alzheimer's Institute; Translational Genomics Research Institute.

**Specific Aims:**

Aim 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).

Aim 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.

Aim 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:**

Now in its 17th year, "The Longevity Study: Learning from Our Elders Cohort" (LCS) is a unique Phoenix metropolitan area-based longitudinal study of biopsychosocial dynamics, lifestyle, physical activity, and cognitive function in successful aging of independent, community-dwelling, older individuals. With AAC supplemental matching grant support the LCS expanded clinical assessments, categorization and phenotyping and added collection of biological samples.

Since its inception, the LCS has enrolled 1614 participants, and currently follows 479 active participants. The average age of participants is 81.4±8.2 (Median = 81) years; and 33% of active participants are ≥ 85, the "oldest old", a rapidly growing demographic in AZ and the U.S. in whom there is a paucity of data regarding bio, and psychosocial factors associated with successful aging. Availability of additional data and biospecimens provided through AAC (matching) grants, and co-enrollment and referral of participants to impactful cognitive aging and biomarker studies (e.g. see below regarding referral and co-enrollment with the internationally renowned Brain and Body Donation Program, BBDP), will continue to create a synergistic effect of adding value and impact potential for an enhanced LCS database to possess a complete range of quality biopsychosocial data in a unique population, the older and the oldest old. The expanded dataset provides a valuable resource that will be further leveraged to better understand biopsychosocial factors, their inter-relations, and their dynamics that are associated with successful aging, neural resistance and cognitive and functional resilience and reserve.

Finally, validating clinical phenotypes, by assessing the global status of LCS participants, facilitates and supports recruitment, dual/co-enrollment and retention of cognitively unimpaired (CU) participants into other impactful studies such as the BBDP, AZ ADRC and clinical trials. For

example, continuing to facilitate and support dual enrollment between LCS and BBDP serves to support continued enrollment of CU elderly participants, particularly the oldest old, into the BBDP, provides critical cross-validation between these programs, and allows additional opportunities for exciting and impactful science to be undertaken in the subset of dually-enrolled participants who are highly characterized by psychometric, biological, clinical, psychosocial, and, ultimately, pathological (autopsy) data. Additionally, when some participants change status from CU to mild cognitive impairment (MCI) or dementia, or when potential candidates for enrollment (during initial contact or enrollment) are identified with potential MCI or dementia status referrals (clinical and research) can be facilitated, including to other research studies and clinical trials.

**Preliminary Data, Experimental Design and Methods:**

The LCS has 479 active participants (enrolled 1,614 since inception). Approximately annual visits are conducted and new participants are enrolled to offset attrition, which is 4.5% per year (annualized over the 15-years; mostly due to death and moving from AZ). Approximately 70% of participants are female, 311 are ≥80 years of age, 170 are ≥85, 80 are between 90-99, and 4 are 100 years or older. Publications below (Refs 1-10) provide exemplars of the diversity of LCS research, and of the PI's research on explicating factors related to cognitive reserve (Refs 11-14). In the 2021-2022 funding year we had one manuscript from the LCS published (Melikyan et al. Norms and equivalences for MoCA-30, MoCA-22, and MMSE in the oldest-old. *Aging Clin Exp Res.* Epub 2021 May 29*, Ref 15*) which contributes to providing normative data and measures to assess cognitive performance and to detect potential cognitive impairment in the oldest-old (90+ year-olds); an area that has been devoid of good normative data.

**Year End Progress Summary:**

The great progress in FY 2023-2024 is summarized in the table below. We expect to add to this progress by further clinical phenotyping of participants; continuing collection, characterization and biobanking of additional plasma samples (added to samples from >535 participants, and 416 participants ApoE-e4 typed) from newly enrolled and returning participants.

| | **Pre-Screens** | **TICS** | **New Enrolled** | **Phone Visits - Original** | **Phone Visits - Annual** | **In-Person Visits - Original** | **In-Person Visits - Annual** |
|---|---|---|---|---|---|---|---|
| **FY22-23** | 54 | 47 | 46 | 1 | 152 | 45 | 242 |
| | **Blood Draws – Initial*** | **Blood Draws – Repeat*** | **CDRS – Original*** | **CDRs Annual – Initial*** | **CDRs Annual – Repeat*** | ***numbers do not include 88 participant who are co-enrolled with BBDP*** | |
| **FY22-23** | 100* | 147* | 37* | 20* | 104* | | |
| | **Phone Consents - Original** | **Phone Consents - Annual** | **In-Person Consents - Originals** | **In-Person Consents - Annual** | | | |
| **FY22-23** | 44 | 50 | 76 | 141 | | | |

**Progress made on Specific Aim 1** –

During the 2023-24 funding period, we continued to require that all new LCS enrollees have a study participant partner to undergo the CDR interview. Previously enrolled participants who did not meet thresholds on cognitive testing and trajectory were also required to have a study partner to undergo the CDR interview. More than 750 CDRs have been performed in the LCS (excluding those of BBDP co-enrolled participants, N=88). As expected, the vast majority of active LCS

participants (>96%) are classified as without dementia. The incidence of minimal or mild cognitive changes/impairments are, thus far, in the 25% range, which is within the expected range for participants who are, on average, in their 80's and of whom >49.3% are above age 84 years.

**Progress made on Specific Aim 2** –
Response to requesting LCS participants to opt-in to donate ~30 cc of plasma for aliquoting, banking of plasma (and sending the buffy coat to TGen for ApoE4-typing per collaboration supported by a previous AARC grant to TGen in 2017-2018) has been outstanding. We had aimed for ~65% of participants opting in to donate plasma, however, to the credit of the participants, >90% of eligible participants have donated a plasma sample. In addition to plasma samples from 535 participants banked so far (including for participants co-enrolled with BBDP), 416 participants have been typed for ApoE-e4 status (88 via co-enrollment with BBDP). Since June 2023 (excluding 81 active BBDP co-enrolled participants) the LCS has supported 104 new participant blood draws and 116 draws in participants who have previously donated.

**Progress made on Specific Aim 3** –
Dr. Atri collaborated with Dr. Chen to explore a variety of ML analyses utilizing BBDP longitudinal cohort data. Application and validation of ML methods is an ongoing aim.

In 2023-24 the LCS data and grant supporting the following poster presentations: 1) AAC 2023 Conference Poster – Association between subjective memory complaints and neuropsychological test performance; Midwestern Clinical Psych Student - McCall Conley; investigated whether domain-specific subjective memory complaints are associated with neuropsychological measures of episodic memory, executive function, attention, language, and visuospatial function; 2) Banner/ASU Neuroscience Scholars Program – Association between the cognitive reserve and subjective memory complaints, Afzal Ariff; investigated (summer 2023) whether the Cognitive Reserve Index Questionnaire (CRIq) was associated with domain specific subjective memory complaints and the strongest correlations were found with the domains of language ($r = -0.43$) and memory ($r = -0.60$). Currently two scholars are working on LCS projects.

A manuscript (led by Dr. Malek-Ahmadi) that supports that affective fluctuations in depressive and anxiety symptomatology can predict cognitive decline in older adults is being revised for publication. In 817 cognitively unimpaired LCS participants (age range 53-102 years) assessed longitudinally, we measured cognition, depressive, and anxiety symptoms. Intrasubject standard deviation (ISD) quantified year-to-year variability of affective measures. Independent mixed-effects models, adjusted for age, education, and sex, showed that greater variability in depression and anxiety symptomatology was associated with cognitive decline. Exploratory analyses combined models to assess for additive versus additive and synergistic effects, showed that only depressive symptom variability was significantly associated with cognitive decline; interaction of depressive and anxiety variability was not a significant predictor of cognitive decline.

Additionally, in 2023-24, Dr. Malek-Ahmadi submitted, in response to the Notice of Special Interest (NOSI) NOT-AG-21-039 Understanding Alzheimer's Disease in the Context of the Aging Brain, an NIH grant proposal titled "Plasma TDP-43 Associations with Age-Related Subjective Cognitive Complaints and Neurodegeneration". This proposal leverages LCS participants and data to determine whether plasma TDP-43 is associated with age-related changes in cortical volume and thickness, and whether it is associated with subjective cognitive complaints (SCCs) which might reflect age-related cognitive changes.

In FY2023 additional (not including TGen and BBDP), LCS collaborations/data included: 1) Sydney Schaefer, PhD – Arizona State University (Associate Professor), incorporated her motor task into all LCS annual assessments; collected data on >150 participants to date; 2) Kacie

Bauer, CPhil – New Mexico State University (PhD Student, Advisor – Andrew Conway), is collecting data on a computer-based executive function task on 200 participants and sharing LCS data to accompany this; data collection began in 2024.

The LCS remains very successful referring participants to ongoing research studies (~150-200 referrals/year to AD and PD clinical/biomarker trials), including BBDP (~40-60/year), and to contributing to clinic-neuropathological correlation and biomarker validation in AD/ADRD. We will continue to refer and co-enroll LCS participants in impactful research studies, and also to leverage this expanding rich dataset with biosamples for collaborative projects and funding sources for clinico-biomarker correlations discovery and as a basis for growth opportunities as a major AZ-based biorepository, biomarker instrumentation and integrative bioinformatics center.

# ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Enhancement of Arizona Alzheimer's Consortium Resource Sharing and Recruitment.** Alireza Atri, MD, PhD, Thomas Beach, PhD, Parichita Choudhury, PhD. Banner Sun Health Research 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 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 BBDP), form substantial infrastructure and cores for impactful multi-institutional, multi-disciplinary resources, collaborations, and programs for AD/ADRD basic, translational and clinical research.

For example, the BBDP database includes 2,275 brain autopsies, 943 body autopsies, 1687 CSF samples, and 1914 serum samples. Participants with autopsy data and at least one assessment in the data base included data for 1021 participant MMSEs, 1017 participant neurologic exams, 1039 participant neuropsychological exams, and 1100 participant-specific movement exams. Clinicopathologic diagnosis available include 418 cognitively unimpaired controls, 935 with AD, 257 with PD, 171 with DLB, 182 with Vascular Dementia, 82 with Hippocampal Sclerosis, and 54 with FTLD-TDP.

The AAC/ADRC continue to provide a world-leading scientific resource of longitudinal and neuropathological data, brain and body tissues for the study of AD and related disorders (ADRD), including Parkinson's disease, Lewy Body Disease, Vascular Brain Injury, in their Brain and Body Donation Program; and, particularly in the last 5 years, have 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.

**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 outcomes of this grant provide the shared resources needed to help advance the study, early detection, tracking, diagnosis, treatment and prevention of AD and ADRD, develop new research leaders, help find an AD/ADRD prevention therapy as soon as possible, and establish the roles of blood-based and fluid biomarkers in these endeavors. This will contribute significantly to the development of shared resources that support AD and ADRD relevant research and provides our scientists much greater chances to find and accelerate approaches to treat and prevent AD and ADRD.

**Year End Progress Summary:**

There has been outstanding progress in 2023-2024 (FY 2023) 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.

In 2023, the BBDP 1) added 92 new participant donors; 2) conducted 2,254 annual assessments in 564 living participants; 3) conducted 59 rapid autopsies with an average time of 3 hours from death to autopsy. The program also distributed a total of 20,000 biospecimens through 255 shipments to researchers all over the world, a total of more than 1,000 shipments in the last 5 years. In 2023, samples were shared with 117 Arizonan scientists, while 116 shipments were to scientists in 19 other US states, with 20 shipments to international scientists based in 10 different countries. In 2023, the program contributed to over 30 scientific publications (see list of overall publications in AAC progress report) and continued to support more than 60 grant-funded research projects and grant proposals. The program also collected skin biopsy samples from 55 participants, blood samples from 406 participants and cerebrospinal fluid from 58 participants. Eleven BBDP participants also had PET scans for plaques (amyloid), tangles (tau), synapses (SV2A) and/or structural brain changes (MRI), which add up to >650 scans over the past 5 years.

In our AZ ADRC Clinical Core (sites at BAI-Phoenix, BAI-Tucson, BSHRI, Barrow Neurological Institute, Mayo Clinic Scottsdale), we have 1,557 active National Alzheimer's Coordinating Center

(NACC) Uniform Data Set (UDS) assessed participants, including 644 Actively followed Clinical Core participants (644 according to the April 1, 2023 NACC UDS monthly report for our center) and hundreds of participants in affiliated studies. These including 20 participants in LEADS (Longitudinal Early-onset Alzheimer's Disease Study), 502 participants with uploaded NACC data in our affiliated Arizona APOE Cohort, 103 participants with uploaded NACC data in our affiliated Brain and Body Donation Program (BBDP), and 318 affiliated BBDP participants whose data have not been uploaded to NACC.

Overall, our actively UDS-assessed participants include a) 712 in the BBDP (518 of whom are cognitively unimpaired) to support studies that will ultimately capitalize on neuropathological assessments and high-quality brain tissue; b) 1031 cognitively unimpaired APOE4 homozygotes, heterozygotes, and non-carriers to support the early detection and tracking of AD, the study of AD risk, resilience, and resistance factors and normal brain aging, and the design of prevention trials; c) 68 with a clinical diagnosis of probable AD dementia, 58 with other dementias, 172 with MCI, and 1,259 cognitively unimpaired participants to support a range of clinical disease stages and diagnoses; and d) 166 Hispanic/Latino, 46 Native American, and 23 Black/African American research participants to support the study of these underrepresented groups.

Within the Clinical Core itself, our active UDS-assessed participants with NACC-uploaded data include a) 311 in the BBDP participants (250 of whom are cognitively unimpaired), b) 339 cognitively unimpaired APOE4 homozygotes, heterozygotes, and noncarriers, c) 43 with probable AD dementia, 24 with other dementias, 68 with MCI, and 499 who are cognitively unimpaired; and d) 94 Hispanic/Latino (including 3 with probable AD, 1 with other dementias, 8 with MCI, and 82 unimpaired), 41 Native American (including 1 with probable AD, 3 with other dementias, 4 with MCI, and 33 unimpaired), and 11 Black/African American research participants. As per our A1 UDS visit enrollment report, since September 1, 2021, we have 476 participants with A1 UDS visits entered in NACC (of these 94 are Hispanic/Latino and 41 are Native American participants), and currently also have 146 participants with site completed A1 visits that are pending entry completion in the NACC UDS database. Notably, we have 103 currently enrolled Hispanic/Latino participants (27 new in Year-3) of whom 94 have fully uploaded data (with A1 visits) in the NACC UDS database. We also have 43 currently enrolled Native American participants (6 new in Year-3) of whom 41 have fully uploaded data (with A1 visits) in the NACC UDS database.

We also have made excellent progress on ATN (Amyloid, Tau, Neurodegeneration)-related scan and biofluid acquisition with a high rate of participation and ADRC scans completed. Overall, 122 of 420 total scans were completed from July 2023-April 2024. We have, thus far, acquired amyloid/tau scans and brain MRIs in 31 Hispanic/Latino ADRC enrollees. As part of the Biomarker Core, we have completed a total of 85 scans in 29 Hispanic/Latino participants (29 in Year 3); 27 participants have had a complete set of all three scans (brain amyloid PET, tau PET and MRI) acquired. Three Hispanic/Latino participants have completed MRI scans only, and there are 28 scans scheduled/pending completion. Also, thus far, we have acquired amyloid or tau scans for 19 Native American ADRC enrollees (15 with a complete set of amyloid PET, tau PET and MRI scans; and overall 18 amyloid PET, 18 tau PET, and 17 MRI scans in Native American participants). After a pause to gain community consensus and alignment we have resumed Medstar referrals and new Native American participant enrollments. Our progress demonstrates our ability to recruit Native American individuals into the Clinical Core and to acquire vital scans

to provide data and blood samples to support the validation and generalizability of amyloid and tau BBBMs in this underrepresented group.

Regarding brain donations, our overall autopsy consent rate is excellent at 49% (311/634). This includes a 39% (17/43) rate for participants with probable AD dementia and a 50% (34/68) rate for participants with MCI. Autopsy completion rate is high at 93%. From July 2023-April 2024, the Neuropathology Core performed 53 autopsies, including 18 on subjects enrolled in the ADCC/ADRC Clinical Core. Our extremely large BBDP, which includes those in our clinical core and affiliated BBBP, which includes comprehensive UDS and other annual assessments, brain and usually body tissue donation, extremely short post-mortem intervals, and comprehensive neuropathological assessments, remains a particular strength of our ADRC and overall Consortium.

Finally, we maintain close collaborations with our other AZ ADRC Center Cores. We hold quarterly clinical-pathological correlation conference with our Neuropathology Core; meet monthly with our ORE core to address diversity issues, outreach and recruitment of underrepresented groups; meet biweekly to review enrollment progress, harmonize, and enhance quality assessment and assurance; to work with our Data Core on enhancing our database query platform and tools, and with our REC to provide educational opportunities including lectures to trainees; and to meet monthly with our Administrative Core.

# ARIZONA ALZHEIMER'S CONSORTIUM
# 2023-2024 Scientific Progress Report

**Trajectories of Clinical Symptoms and Associations with Pathology in Lewy Body Spectrum Disorders.** Parichita Choudhury, MD, Nan Zhang, Msc, Kewei Chen, PhD, Thomas Beach, MD, PhD, Charles H Adler, MD, PhD, Alireza Atri, MD, PhD. Banner Sun Health Research Institute; Mayo Clinic Arizona; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

**Specific Aims**:

1) Aim 1: To further define longitudinal neuropsychological profiles in patients with clinicopathologically confirmed diagnosis of Dementia with Lewy bodies (DLB), Parkinson's Disease Dementia (PDD) and Alzheimer's Disease (AD) in relationship to underlying pathology.
2) Aim 2: To further define domains of neuropsychiatric symptom (NPS) changes in pathologically defined Lewy Body Dementias (LBD) and related disorders and their relationship to survival.
3) Aim 3: To continue development of a readily interpretable composite score to predict disease burden (as manifest by Unified Lewy body staging system or Lewy body density) based on validated, brief and standardized measures of cognition and function via machine learning/artificial neural network (ANN) approaches.

**Background and Significance:**

LBD, comprised of DLB and PDD, share pathophysiological substrates and clinical features, with current diagnostic criteria differentiating the two based on relative timelines of emergence of symptoms. Neuropsychological profile is found to be useful in distinguishing mild cognitive impairment (MCI) progression to neuropathologically confirmed AD vs. DLB. DLB is characterized by deficits in semantic fluency, attention, and visuospatial construction deficit, whereas AD markers include episodic and recognition memory deficits. However, the affected cognitive domains overlap between both clinically and pathologically defined dementia subtypes and lack diagnostic accuracy. Among LBD, there is a dearth of research defining longitudinal evolution of cognition beyond 2 years in patients with autopsy confirmed DLB.

NPS are frequent in AD dementia but a higher NPS burden is found in DLB. Lewy body (LB) pathology frequently co-occurs with AD pathology and may not meet neuropathological criteria for DLB (ADLB). Previous studies have shown that both ADLB and DLB cases have faster cognitive and/or functional decline compared to AD. However, the differences in NPS severity over disease course and survival in these pathologic subgroups is not well understood. We investigated changes in NPS severity over time using the Neuropsychiatric Inventory-Questionnaire (NPI-Q) previously, comparing neuropathologically defined cohorts of AD (without LB), ADLB, DLB and controls. We found increased early NPS in ADLB cohort.

LBDs can present with overlapping prodromal, cognitive dysfunction, motor, autonomic or neuropsychiatric symptoms leading to challenges in diagnosis, management and clinical trial design. Corollary to that, presence of pathological Lewy bodies may not manifest clinical symptoms (such as in ILBD), indicating latent or preclinical disease stage, or variability in individual response to injury and reserve. Impairment in each domain in LBDs may be inter-dependent, be mediated or moderated by other domains and may not represent direct manifestations of underlying pathology. Some studies suggest that increasing cognitive impairment, neuropsychiatric symptoms and motor impairment correlate with higher stages of

Lewy body pathology. A more comprehensive characterization of the clinical trajectories, symptom interaction and associated pathological severity would allow for identification of clinical trial end points and monitoring.

**Experimental Designs and Methods:**

Subject Inclusion/Exclusion Criteria: Cases included in this analysis span the entire spectrum of Lewy body pathologies in the AZSAND database. For Aim 1, cases are excluded if they have only one neuropsychological evaluation. For Aim 2 cases with one neuropsychiatric inventory questionnaire (NPI-Q) are excluded. For Aim 3, cases are excluded if only one measure is available and if interval between last assessment and death is greater than 2 years. Statistical Analysis for cognitive and NPS trajectories: Neuropsychological data is extracted for each cognitive domains and converted to age and education matched scales (as appropriate). Clinical Scales: Demographic information are included. Clinical features described in aggregate include presence of REM sleep behavior disorder, cognitive fluctuations, visual hallucinations, autonomic dysfunction. Several scales are considered and explored for a unified composite risk score. Scales considered as components of Lewy body score include: 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). Ongoing Composite score determination: Previously introduced, validated, and utilized composite score approaches, including those in our Alzheimer's Prevention Initiative (API) trials such as the Colombian Autosomal Dominant Alzheimer's Disease (ADAD) trial, and the Generations trials are considered. Using similar composite score construction approach, a composite score is being developed for this project. Our procedures combine feature selection (tests with zero weights are filtered out) and optimization together. To examine the generalizability of the constructed composite score, we will randomly divide the data as 70% training, 15% validation and 15% for separate testing datasets (with group membership balanced in each). The same cross-validation scheme will also be used for the machine learning approach below. Several ML algorithms and quantitative prediction models were explored and compared: primarily artificial neural network (ANN), partial least square regression (PLSR), support vector regression (SVR), relevance vector regression (RVR) and ensemble forest regression (EFR) with leave-one-out (LOO) scheme

**Year End Progress Summary:**

Overall, excellent progress was made during FY2023 (July 2023-June 2024) toward accomplishing the aims of this ongoing project.

In totality, cases span the entire spectrum of Lewy body pathologies in the AZSAND databases (PD including PDD (n=277), DLB (n=189), Alzheimer's Disease with Lewy-type synucleinopathy (n=291) and ILBD (n=134)). Each group shows a baseline MMSE of 26.3 (PDD), 22.6 (DLB), 22.6 (AD with Lewy bodies) and 25.3 (AD). Preliminary linear modelling showed faster decline in AD with Lewy bodies group compared to other groups in domains of memory. The ADLB group averaged highest for NPI-Q initially but trajectory changes were more prominent for DLB (See Figure 1a, below, *presented at the American Academy of Neurology, AAN international conference)* (Aims 1 and 2).

A series of quantitative prediction modeling and ML algorithmic analyses included a total of 234 subjects with neuropathological finding of Lewy bodies at autopsy who were classified as Cognitively Unimpaired or Mild Cognitive Impairment (MCI) after their first BBDP study clinical

evaluation. Of these, 143 subjects had complete scores for 32 of 46 measures (clinical, cognitive, behavioral and functional) that were utilized as predictors of LB pathology. Olfactory function was assessed using the University of Pennsylvania Smell Identification Test (UPSIT). LB severity was assess by the Unified Staging System for Lewy Body Disorders (USSLB). Several ML algorithms and quantitative prediction models were explored and compared: primarily artificial neural network (ANN), partial least square regression (PLSR), support vector regression (SVR), relevance vector regression (RVR) and ensemble forest regression (EFR) with leave-one-out (LOO) scheme. Game-theory based Shapley methods assessed the impact, including rankings, consistency and magnitude, of model predictors. RVR predicted aggregate LB density with large effect size ($R^2$ =0.691, p<0.00001). ANN predicted USSLB severity stage with large effect size ($R^2$=0.74, p<2.5e-43). All other ML algorithms/models provided substantial prediction as well. Across all these 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. *These preliminary and exploratory results support the utilization of ML techniques/models to assess LB pathologic burden with key measures collected in relatively small samples (Aims 1-2), and has been accepted for presentation at the Alzheimer's Association International Conference (AAIC) in Philadelphia (July-August 2024).*

In exploratory analysis, we used covariance-based Structure Equation (aka Causal) Modeling (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 OIF (olfactory) as predictors and account for their measurement errors. With the following SEM configuration to predict LB (see Figure 1b, below). We obtained goodness of fit indices such as Chi-square test p-value of 0.285 (non-significant suggesting the model is plausible), RMSEA (root mean square error of Approximation) of 0.0345 (below 0.05 indicative of a close fit of the model in relationship to the degrees of freedom) and CFI (comparative fit index) of 0.9913 (>0.95) excellent fit of the model to the data (Aims 1-3).

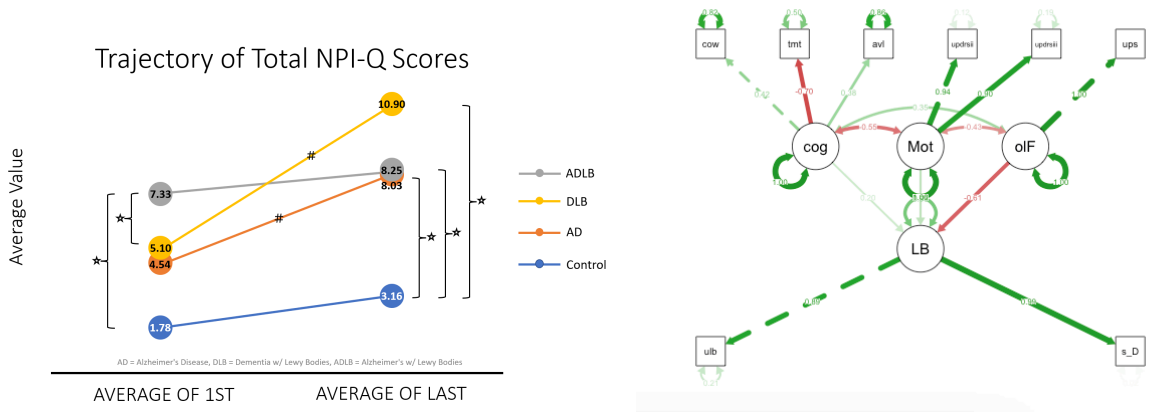



Figure 1: a) Trajectories of NPI-Q in ADLB; b) SEM latent variable causal modeling analysis of the relationships between Lewy Body disease Pathology and cognitive, motoric, olfactory and clinical latent and manifest variables.

# ARIZONA ALZHEIMER'S CONSORTIUM
# 2023-2024 Scientific Progress Report

**Patient-based Postmortem Fibroblast Banking for Translational Research**. Geidy Serrano, PhD, Thomas Beach, MD, PhD, Rita Sattler, PhD, Lalitha Madhavan, Suet Theng Beh, PhD. Banner Sun Health Research Institute; Barrow Neurological Institute; Arizona Alzheimer's Consortium; University of Arizona.

## Specific Aims:

Aim 1: To expand the fully characterized scalp tissue-derived fibroblasts from donors with neurodegenerative diseases or without neurodegenerative diseases to increase the variety and number of cryogenic cells in different neurodegenerative diseases as well as control groups.
Aim 2: To generate and bank human iPSC lines generated from eight of our banked cases.
Aim 3: Develop and validate protocols to directly reprogram human fibroblasts to neurons and other cells, particularly for AD and PD cases.

## Background and Significance:

Alzheimer's disease (AD) and Parkinson's disease (PD) are prevalent neurodegenerative disorders in the aging population. Despite significant advancements in disease understanding and diagnosis over the past three decades, effective disease-modifying treatments have yet to be established. To develop more effective treatments, improved experimental models are needed to better recapitulate the disease pathways in human brains. Therefore we propose baning skin fibroblast to use as a model or reprogram for alternative cell models. Skin fibroblasts are the most frequently used somatic cell types for stem-cell-based procedures. At BSHRI, the Brain and Body Donation Program (BBDP) banks postmortem tissues from 60-80 autopsy cases a year. Since the program has access to scalp tissues at autopsy, it can be leveraged as an invaluable source of skin samples to make fibroblasts. Importantly, the participants of BBDP were enrolled in a longitudinal aging study and received regular clinical and neuropsychological assessments, allowing for a comprehensive analysis of the relationship between neurodegenerative disease and aging. The use of well-examined postmortem tissue-derived fibroblasts and cells can provide valuable insights into the pathophysiology of neurodegenerative diseases.

Induced pluripotent stem cells (iPSCs) have emerged as a promising tool for modeling neurodegenerative diseases (1-3) and is the most common use so far of our biorepository. However, there are limitations to using iPSCs, such as genetic variability, incomplete reprogramming, losing epigenetic memory and not fully maintaining the complex microenvironment and disease pathology found in human brains.

## Year End Progress Summary:

Since 2018, fibroblasts from 104 cases have been banked, totaling 2.105 billion fibroblasts. During the current funding period, we have successfully banked fibroblasts from 12 scalp tissues out of 20 donor cases processed, totaling 153 million fibroblasts from those 12 cases. The most common diagnosis among these cases was AD, accounting 20%, followed by 14% of PD, and 15% of cases with Mild Cognitive Impairment (MCI, 15.2%). For APOE genotypes, most banked cases had the APOE 3/3 genotype 56.6%, 23% had the APOE 3/4 genotype, and 4.0% had the APOE 4/4 genotype.

Fibroblasts from P1 to P3 have been collected and cryopreserved. The success rate for scalp explant culture was 70-60%. All banked P3 cells have full characterization of fibroblast markers (FAP, FN1, THY1, VIM, KRT14) and are routinely checked for mycoplasma contamination every 3 months.

Since 2018, we have provided a total of 64 fibroblast lines to research groups and biotech companies to study AD, PD and FTLD. During this grant year, we have provided a total of 38

fibroblast lines to research groups and biotech companies. Ten fibroblast lines were sent to three groups for reprogramming, while one group is conducting genomics and transcriptomics studies, as well as reprogramming. We sent five lines of fibroblasts to the Human Stem Cell and Neuronal Differentiation Core at the Dan Duncan Neurological Research Institute, collaborating with Dr. Bajic and reprograming rate was poor. Cedars-Sinai Medical Center successfully reprogrammed two lines of fibroblasts and characterized them. Reprogramming of three lines of fibroblasts at the University of Arizona, collaborating with Dr. Madhavan, who was able to reprogram 2 out of the 3 cases and generate multiple clones per case.

As we encountered challenges in reprogramming our banked fibroblasts, we recognize that comprehending the aging features of banked fibroblasts and the underlying biological mechanisms may hold the key to unlocking the potential for successful reprogramming or utilization of our cells. Therefore, our primary goal for this grant year is to understand the aging features present in the culture of our banked fibroblasts from aged and diseased donors. We aim to develop a deeper understanding of the aging traits observed in cultured fibroblasts obtained from older and diseased donors.

In this grant year, we are examining whether and how senescent cells are involved in this process. Our approach involves conducting a comprehensive investigation into the biochemical, morphological, and metabolic changes occurring in senescent primary fibroblasts derived from aged and diseased donors. Given that the fibroblasts acquired from our bank are donor and age-specific, advancements in characterizing morphological changes and bioenergetics could significantly enhance the utilization of fibroblasts, particularly in the fields of reprogramming and personalized medicine (Fig1).

The experiments and analysis are currently in progress. Preliminary data indicate that replicative senescence in cultured fibroblasts during aging is characterized by flattened cellular morphology, cell enlargement. By passage 15, control fibroblasts show irregular shapes and increased cell size. AD fibroblasts begin to show enlargement and morphological changes as early as passage 9. By passage 15, AD fibroblasts display pronounced signs of senescence, such as increased granularity, flattened morphology, enlargement, and a marked decrease in cell density (Figure 1). The doubling time analysis (Figure 2) reveals that AD fibroblasts have a significantly longer doubling time compared to control fibroblasts at passage 15 ($p < 0.01$). No significant differences were observed between the control and AD groups at passages P3 and P9. Across all passages, the doubling time increased significantly with passage number ($p < 0.0001$), indicating an overall trend of slower cell proliferation in later passages.

Our objective is to identify the passage or conditions that may lead cells to metabolic dysfunction and altered bioenergetics, enabling us to analyze age- and disease-dependent changes. In future studies, we will conduct in-depth metabolic profiling of these fibroblasts at different passages. This will involve analyzing mitochondrial function, glycolysis rates, and overall cellular bioenergetics. By identifying specific metabolic signatures associated with aging and disease, we can optimize reprogramming protocols to enhance their efficiency. Additionally, we will investigate the specific pathways involved in cellular senescence, such as the p53-p21 and Rb-p16$^{ink4a}$ pathways. By targeting these pathways with small molecules or genetic interventions, we aim to mitigate senescence-associated features and improve reprogramming efficiency.

We aim to publish the results before the end of this year, to promote the utilization of our cell lines in scientific research. Also, we will actively participate in conferences to have opportunities for collaboration with scientists utilizing cells and reprogramming techniques for disease modeling. These conferences provide networking opportunities with researchers worldwide and the potential for collaborations with professionals from the biotech and pharmaceutical areas. We aim to increase awareness of our biorepository, foster collaborations, and establish partnerships with experts from academia and industry.

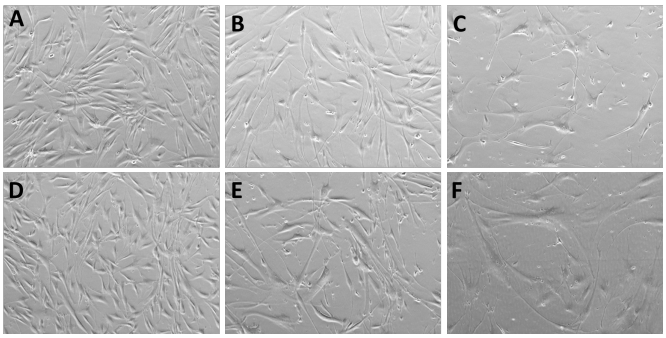



**Figure 1: Progressive morphological changes of control and Alzheimer's Disease (AD) fibroblasts at different passages.** (A-C) Representative images of control fibroblasts at passages 3 (A), 9 (B), and 15 (C). These fibroblasts show typical elongated, spindle-shaped morphology. At passage 15 (C), the control fibroblasts begin to show irregular shapes and enlarged cell bodies, indicating early signs of senescence. (D-F) Representative images of AD fibroblasts at passages 3 (D), 9 (E), and 15 (F). At passage 9 (E), AD fibroblasts start to show enlarged cells and irregular shapes. By passage 15 (F), the cells display pronounced signs of senescence, such as increased granularity, flattened morphology, enlarged cell size, and a significant decrease in cell density.

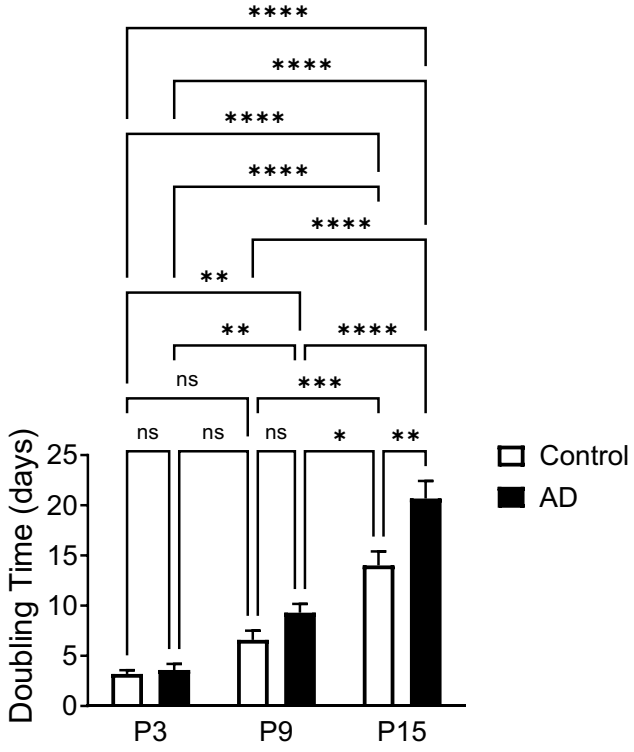



**Figure 2. Growth rate analysis of control and Alzheimer's Disease (AD) fibroblasts.** The bar graph shows the growth rate control and AD fibroblasts at P3 (P2 to P3), P9 (P8 to P9), and P15 (P14 to P15). Data are represented as the mean ± standard error of the mean (SEM) for each group. Statistical significance was determined using two-way ANOVA and Tukey's multiple comparisons test (ns: not significant, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$).

# ARIZONA ALZHEIMER'S CONSORTIUM
# 2023-2024 Scientific Progress Report

**A Human Brain Single-Cell Suspension Resource.** Geidy Serrano, PhD (PI), Thomas G. Beach, MD, PhD, Ignazio Piras, PhD (Consultant), Matthew Huentelman, PhD (Consultant), colleagues from each of the participating Arizona Alzheimer's Consortium sites. Banner Sun Health Research Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

## Specific Aims:

Aim 1: To provide the foundation of a shared resource of separated cells to researchers within and outside Arizona.
Aim 2: Phenotypically and Biochemically characterize single cells and phenotypically-specified populations of cells from single-cell suspensions created with an optimized standardized method (from Specific Aim 1).

## Background and Significance:

Biochemical analysis of human neurodegenerative brain tissue, especially from Alzheimer's disease (AD) and Parkinson's disease (PD) patients, has produced much of what is known about these conditions, and has led to the major FDA-approved therapies. The typical approach has been to homogenize whole pieces of brain tissue and separately characterize the proteins, RNA, DNA and other macromolecules within. While this has been sufficient to identify large changes, there is very little ability to identify small changes, or changes in small subsets of cells. Furthermore, neurodegenerative disease often leads to massive losses of the targeted and disease-relevant cells, for example the entorhinal cortex layer II stellate neurons or substantia nigra pigmented neurons. Whole-homogenate analysis of such brain regions can give completely misleading results, as any biochemical constituent that is selectively localized to the depleted cells will appear to be "down-regulated", whereas in fact it has most likely been lost only as an "innocent bystander". Also, a relevant loss or increase might be completely missed, if the biochemical entity is found in many cell types, diluting the 'lost" signal from the cell of interest, especially if that cell type is uncommon or rare. To effectively investigate the biochemistry of neurodegenerative disease in the brain, with its thousands of different cell types, we must first separate the cells, and study them as phenotypically-defined populations and even as individuals. In recent years, methods have been developed that allow an initial creation of single-cell suspensions from solid tissue followed by analysis of phenotypically-defined cells sorted on the basis of cell-type identifying proteins or RNA expression. Some groups have already published intriguing results from AD brain cells, but as yet there has not been a comprehensive exploitation of these novel technologies utilizing postmortem human brain. This set of experienced neuroscience investigators, together with a unique rapid-autopsy brain tissue resource, are well-suited to apply these methods on a large scale to AD and other neurodegenerative brain diseases.

## Year End Progress Summary:

We currently have WSDS generated from 178 cases from fresh brains, 20 of those collected this funding year. On average we collect 10.0 million cells/gram of tissue. Final suspensions are aliquoted for tissue banking in cryopreservative solution and stored at -80°C and for quality control (QC) assessments. As previously reported single cell suspensions have a diverse cell population, by nuclear morphology typically including approximately 40% neurons, 25% astrocytes (Figure

1), 21% microglia, 5% oligodendrocytes, and 4% endothelial cells (Serrano, et al 2021). We continue to promote the cell core in virtual and in person meetings and keep working in projects using this samples collaborating with Dr. Piras at Tgen, Dr. Lee's group in Harvard and Dr. Ishihara from Eisai.

During this last funding year, we also developed a new protocol that allow us to generate suspension from frozen tissue and performed single nuclei prep that allowed us to compare whole cell preparation vs nuclei preps, demonstrating that nuclei preps only allow us to study 25% of the cell genetic signatures. This new protocol using frozen samples seems to be more efficient, allowing us to collect 10,000 cells per 100mg of frontal gray matter. On average we can detect over 300 million of gene reads per case, and approximately 150,000 reads per cell. It is well known that people over 70 years might have multiple neuropathological pathological changes at death. Another advantage of this new protocol is than rather than collecting samples from cases at autopsy, still pending a pathological evaluation, we could be more selective and only use cases that were already fully characterized. Next year, we plan to expand our studies using this new protocol.

In addition, the suspensions that we have collected and characterized over the years were used to study astrocyte populations in AD, PD, progressive supranuclear palsy (PSP) and controls using new approaches to analyze complex data set generated from subjects with multiple pathological diagnosis. In short, analysis done this year on astrocyte enriched population included correlation between neuropathology and the differentially expressed genes (DEGs). We found that PSP astrocytes had a larger number of dysregulated genes when compared to CN (1,968). Of those 1,933 were upregulated genes and 35 downregulated. When PSP was compared to AD, we observed a total of 89 genes dysregulated, with 88 of those presenting with upregulation. PSP comparison with PD cases resulted in a total of 243 genes dysregulated, with 239 of those being downregulated in PSP (Table 1). Moreover, dopaminergic and GABAergic synapse pathways seem to be affected on PSP astrocytes when compared to controls, while tight junction proteins and estrogen signaling seems to be affected in PSP astrocytes when compared to ADD. Interestingly, when we look for shared biological processes or genes affected on PSP, PD and AD, we found that ubiquitin pathways were commonly affected in astrocytes in all of these neurodegenerative diseases when compared to controls. This suggest that protein degradation is dysregulated in the astrocytes of all these neurodegenerative disorders. Previous studies have shown how ubiquitin pathways might be affected in neurons from some of these diseases but until now little has been reported about the dysfunction in astrocytes, and possible implications on astrocytes important functions of phagocytic clearance and neuronal repair.

**Reference:**

1. Serrano, G. E., Walker, J. E., Intorcia, A. J., Glass, M. J., Arce, R. A., Piras, I. S., .. Beach, T. G. (2021). Whole-Cell Dissociated Suspension Analysis in Human Brain Neurodegenerative Disease: A Pilot Study. medRxiv, 2021.2001.2008.21249455. doi:10.1101/2021.01.08.21249455

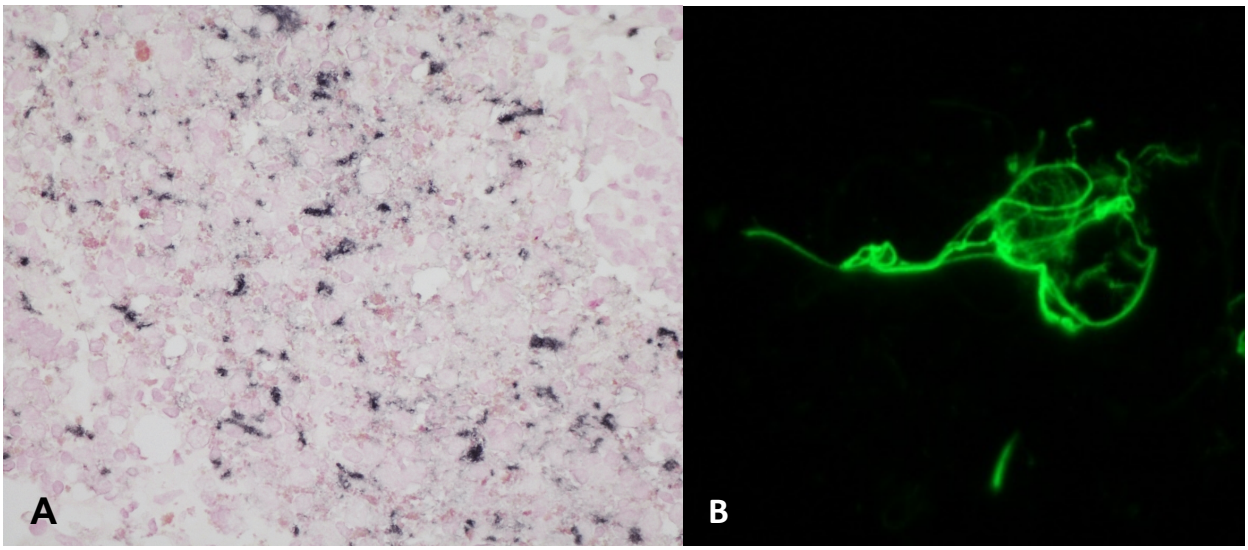



**Figure 1. Single cell suspensions have a diverse cell population.** Using nuclear morphology and astrocyte specific antibodies (GFAP) allowed us to confirm that cell suspensions are composed of 25% astrocytes(A), cells that are resistant to the dissociation process and keep almost full integrity (B).

**Table 1. Number of dysregulated genes for all disease comparisons.**
For all comparisons, adj-pvalue of DEGs is <0.05

| Comparison (number of samples) | No. of DEGs |
|---|---|
| PSP (5) vs. CTL(3) | 1,968 (1,933 upregulated, 35 downregulated) |
| PSP (5) vs. AD (4) | 89 (88 upregulated, 1 downregulated) |
| PSP (5) vs. PD (6) | 243(4 upregulated, 239 downregulated) |
| AD (4) vs. CTL (3) | 754 (749 upregulated, 5 downregulated) |
| AD (4) vs. PD (6) | 4 (1 upregulated 3 downregulated) |
| PD (6) vs. CTL (3) | 540 (4 upregulated, 536 downregulated) |
| PD (6) vs. ILBD (3) | 150 (135 upregulated, 15 downregulated) |
| ILBD (3) vs. CTL (3) | 1 (downregulated) |
| PSP+PD+AD+ILBD (18) vs. CTL (3) | 501(456 upregulated, 137 downregulated) |
| PSP+PD+AD (15) vs. Non-symptomatic (CTL+ILBD)(6) | 816 (636 upregulated, 180 downregulated) |

# BARROW NEUROLOGICAL INSTITUTE
# PROJECT PROGRESS REPORTS

# ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Synaptosome Proteomics to Identify Molecular Signatures in Dementia Spectrum Disorders.** Robert Bowser, PhD, Elliott Mufson, PhD, Lathika Gopalakrishnan, PhD, Patrick Pirrotte, PhD, Karen Fisher, PhD. Barrow Neurological Institute; Translational Genomics Research Institute; Arizona State University; Arizona Alzheimer's Consortium.

**Specific Aims:**

The aim of this research proposal is to perform a proteomic analysis of the frontal cortex from different types of dementia. The specific objectives are:

1. Synaptosome preparations from the frontal cortex of AD, ALS, FTD and non-neurologic control subjects.
2. Perform tandem mass tag (TMT) proteomics using LS-MS/MS to quantify synaptic protein abundance across all samples.
3. Perform a functional analysis of the differentially expressed proteins to identify the biological pathways and processes associated with dementia spectrum disorders and validate key synaptic proteins.

**Background and Significance:**

The proposed research will provide a comprehensive proteomic atlas of synapses from the frontal cortex of different types of dementia by identifying the differentially expressed proteins. While there have been significant advances in understanding the underlying pathophysiology of dementia, the complexity and heterogeneity of the diseases have made it challenging to develop effective treatments. One of the main challenges is the heterogeneity of dementia subtypes, which makes it difficult to identify specific molecular targets that are relevant across all subtypes. Additionally, the brain is a complex and dynamic organ, and changes in synaptic proteins may occur at different rates and times in different brain regions and during disease progression. Emerging evidence suggests that synaptic dysfunction, particularly in the prefrontal cortex and hippocampus, is an early and prominent feature of dementia (5). Synaptic proteins, such as PSD95, synaptophysin, and SNAP25, are critical for synapse formation, function, and plasticity (6). Therefore, continued and more extensive investigation in the expression and localization of synaptic proteins in dementia may provide novel insights into the pathophysiology of the disease and identify novel therapeutic targets.

**Preliminary Data, Experimental Design and Methods:**

In our preliminary analysis, we used a combination of subcellular fractionation methods and mass spectrometry to analyze synaptosomal protein expression levels in the dorsolateral prefrontal cortex (DLPFC) from the postmortem brain tissue samples of individuals with schizophrenia and non-neurological control subjects. Following synaptosome isolation, we extracted synaptic proteins and performed proteomic analysis using an Orbitrap Fusion mass spectrometer. The LC-MS/MS analysis resulted in the identification of 3,509 proteins, of which 464 proteins showed altered expression ($p<0.05$) in schizophrenia in DLPFC. Our results indicate that there are significant differences in the expression levels of synaptic proteins, including synapsins, RAB3A, and DNAJC5, in individuals with schizophrenia compared to controls (Figure 2). Additionally, our preliminary data suggest that there are alterations in several signaling pathways in schizophrenia, including the calcium signaling pathway, the synaptic vesicle cycle, and the dopamine receptor signaling pathway, leading to aberrant synaptic function and ultimately contributing to the pathophysiology of the disorder.

**Proposed One-Year and Long-Term Outcomes:**

**Specific Aim 1: Synaptosome preparation from frontal cortex across dementia subtypes**

The proposed study aims to isolate synaptosomes from the human frontal cortex of AD (n=4), ALS (n=4), FTD (n=4) and gender/age-matched non-neurologic control subjects (n=4). We obtained the appropriate frozen tissue samples from the biorepositories at the Barrow Neurological Institute (Target ALS Core) and Banner Health System (Dr. Beach). The enriched synaptosomes were assessed for purity and integrity using western blot for known synaptic markers and electron microscopy, respectively.

**Specific Aim 2: Comparative proteomic analysis of synaptosomes isolated from frontal cortex of AD, ALS, FTD and control subjects**

Synaptosomes collected were lysed and the protein concentration will be estimated by Bicinchoninic acid assay. The synaptosomal proteins were subjected to reduction, alkylation and trypsin digestion. The digested peptides were labeled using TMTpro 16plex isobaric label reagent following the manufactures' instructions. The samples were analyzed using liquid chromatography-tandem mass spectrometry (LC-MS/MS) at TGen and the data was analyzed using bioinformatics tools such as Proteome Discoverer and Perseus to identify the significantly dysregulated proteins.

**Specific Aim 3: Identify dysregulated pathways in the synapse associated with dementia spectrum disorders and validate key synaptic proteins**

The differentially regulated proteins obtained from the proteomics study were analyzed for the enrichment of biological processes and pathways dysregulated in dementias. Functional analysis of the differentially expressed proteins was performed using bioinformatics tools including Gene Ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis. This also aided in delineating disease-specific molecular pathways that were altered in various dementia disorders. To validate the proteomic findings, immunoblotting and immunohistochemistry will be performed on the same frontal cortex samples. Western blot analysis will be used to confirm the differential expression of selected proteins. Immunohistochemistry will be used to confirm the cellular localization of the differentially expressed proteins.

Our results generated by AARC funding will be used for subsequent grant applications to the NIH to expand upon our initial data, include more dementia subtypes, and explore how synaptic alterations impact the connectome across brain regions and disease specific neurodegeneration.

**Year End Progress Summary:**

We have successfully completed all three Aims of our proposal, though we are currently validating top hits by western blot in the same tissue samples and also in fixed tissue sections by immunohistochemistry.

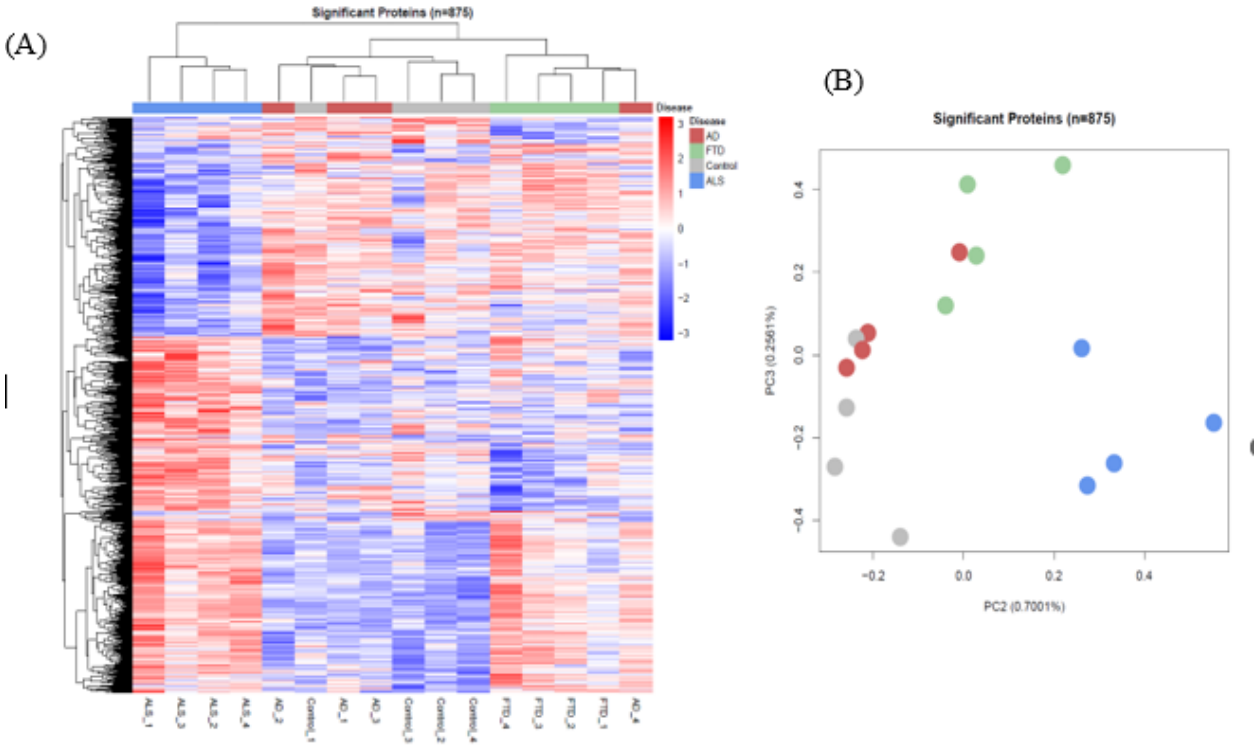


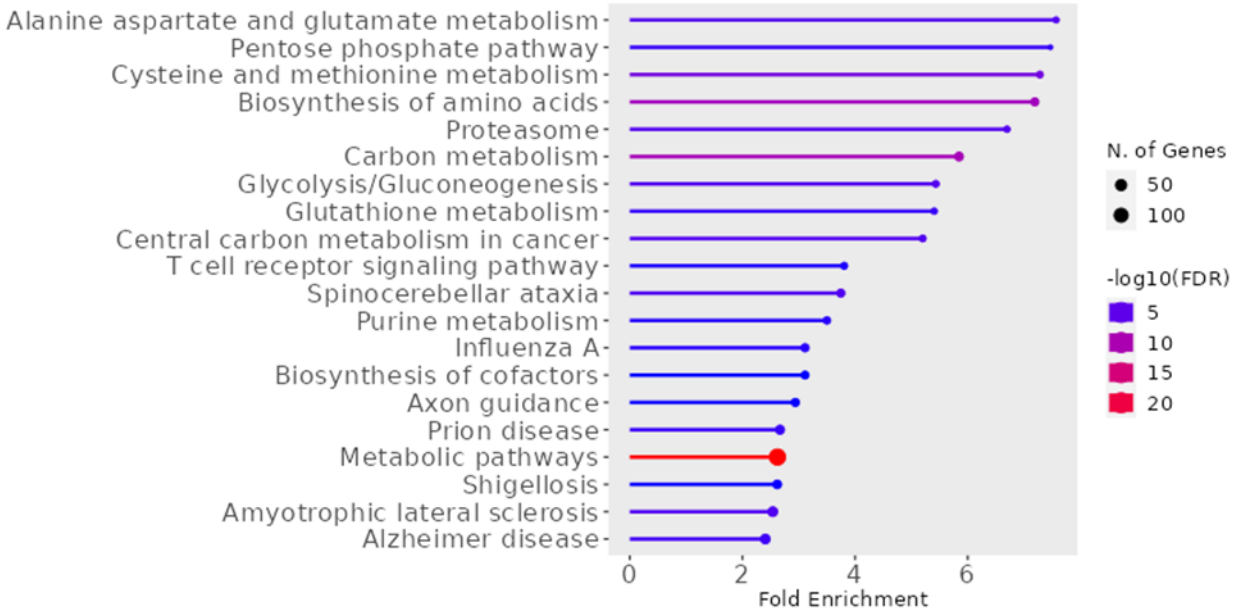

Figure 1: Distinct clustering of significant proteins by disease type reveals clear signatures among different disease groups
(A) Heatmap representing the hierarchical clustering of the significantly expressed differentially regulated proteins across the disease groups. B. PCA of the altered proteins from control and diseased groups.

The quantitative TMT-based global proteomics analysis of synaptosomes from AD, FTLD, ALS and control resulted in the identification of 8,200 proteins. The global proteomics data underwent statistical analysis using an ANOVA, followed by a Tukey post hoc to correct for multiple hypothesis testing (6 pairwise comparisons) and we report 875 proteins to have an ANOVA p-value<0.05 of which 865 proteins have a Tukey post hoc p-value<0.05 in at least one pairwise comparison. Phosphoproteomics analysis resulted in the identification of an average of 1732 proteins and 5131 phosphosites. Of which, 347 phosphosites were found to be statistically significant (ANOVA p-value<0.05) and 349 phosphosites have a Tukey post hoc p-value<0.05 in at least one pairwise comparison.

Using gene ontology analyses, we observed an enrichment of the identified proteins localized to pre- and post-synaptic components such as synaptic vesicles, endocytic zone, spine apparatus and cytoskeleton. Presynaptic proteins such as SNX9 (sorting nexin) and SYNPR (synaptoporin) which are integral to neurotransmitter release and vesicle trafficking. On the postsynaptic side, proteins such as SYNPO (synaptopodin), SHANK2, and GRIN2A (a subunit of the NMDA receptor) were highlighted, reflecting their crucial roles in receptor signaling and synaptic plasticity.

A significant number of proteins show larger changes in their expression levels in ALS vs. Control compared to AD vs. Control and FTLD vs. Control. Proteins such as Retinal dehydrogenase 1 (ALDH1A1), Allograft inflammatory factor 1 (AIF1), Hemoglobin subunit

gamma-1 (HBG1) show significantly higher fold changes in ALS. Major pathways associated with the altered proteins are represented in Figure 2.




Baseline proteomic profile of the control group is closer to that of AD and FTLD likely due to age-related changes or mild cognitive decline, whereas the changes in ALS are more pronounced and distinct. Metabolic pathways such as glycolysis and gluconeogenesis, lipid metabolism and amino acid metabolism were majorly highlighted by the differentially expressed proteins in dementia. Further analyses of the differentially expressed proteins would enable in identifying the key pathways uniquely or commonly dysregulated in the dementia-spectrum disorders. Future studies will expand upon these findings and further replicate the findings in a large cohort of subjects. We plan to publish these initial findings and present the data at national conferences.

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**The Role of Matrin 3 in Dementias.** David Medina, PhD, Nadine Bakkar, PhD, Elliot Mufson, PhD, Sylvia Perez, PhD, Integrated Mass Spectrometry – Shared Resources. Barrow Neurological Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

**Specific Aims:**

Aim 1: Investigating Matrin 3 pathology in human dementia

1a. Perform a quantitative pathological analysis of Matrin 3 pathology with patients with FTD and AD. Further, we will determine the relationship of Matrin 3 pathology with markers of neurodegeneration (e.g. plaques, TDP-aggregation).

1b. Further we will investigate the biochemical changes to matrin 3 from patient samples (e.g. cleavage, solubility) using protein western blot analysis.

Aim 2: Test the functional roles of Matrin 3 in neuronal health and response to neurodegenerative stressors.

2a**.** Test the hypothesis that Matrin3 mutations and loss of function impair synaptic formation and dysregulate synaptic function.

2b. Test the hypothesis that specific MATR3 disease causing mutations and function impact protein solubility, mediate responses to neurodegenerative stressors, and reduce viability.

**Background and Significance:**

Neurodegeneration causing point mutations in Matrin 3 were first identified in amyotrophic lateral sclerosis (ALS) and frontotemporal degeneration (FTD) [1]. Matrin 3 is an RNA- and DNA-binding nuclear matrix protein involved in a variety of functions including RNA transport and splicing modulation. However, the role of MATR3 mutations and matrin 3 function in neurodegeneration is not understood. Mutations in matrin 3 have been shown to cause aggregation, changes in protein-protein binding, and reduction in cell viability. Further, matrin 3 pathology has been reported in sporadic ALS and C9-ALS cases [2]. Importantly, we have recently discovered pathology in cases of frontotemporal dementias as well as Alzheimer's disease (AD), which lacked matrin 3 mutations, thus suggesting an even broader relevance to neurodegeneration. **In this application we have been attempting to fill critical gaps in our knowledge regarding how matrin 3 disease causing mutations and changes in matrin 3 function can induce neurodegeneration in dementias including FTD and AD.**

To understand the functional role of matrin 3 in dementias (FTD and AD) we are employing complimentary approaches to test mechanistic hypotheses. Our prior work identified a novel role for MATR3 protein in the nuclear export of mRNAs via direct interactions with proteins in the Transcription-Export (TREX) complex, with disease causing mutations impacting the nuclear export of mRNAs. In addition to its RNA/DNA binding functions [3], recent studies demonstrated that MATR3 functions as a splice repressor [1,4–8], further supporting a role for MATR3 protein in modulating multiple aspects of transcription and gene expression. In addition, we recently have generated novel knock-in mouse models of matrin 3 mutations P154S [9] and S85C (*in preparation*). These models have produced divergent phenotypes in which the P154S mouse model produced no overt behavioral or pathological phenotypes. In contrast, S85C knock-in mouse model produces motor impairments and pathological hallmarks such as neuroinflammation and loss of matrin 3. Further, transcriptomic analysis demonstrate that genes associated with synaptic function and inflammation are altered in these mice. Our findings are consistent with prior studies that have demonstrated synaptic function influences matrin 3 protein levels, and that matrin 3 functions to modulate peripheral inflammation [10]. Further, we have gathered preliminary data demonstrating pathological matrin 3 pathology in AD. Matrin 3

involvement is in AD is also supported by previous reports demonstrating matrin 3 pathology in AD brains with granulovacuolar degeneration [11] ***We will test the overarching hypothesis that matrin 3 is involved in neurodegenerative dementias, caused by mutations or stressors, and leads to molecular changes that contribute to disease onset and progression.***

**Preliminary Data, Experimental Design and Methods:**

**Matrin 3 Pathology in Dementias:** We have previously optimized staining conditions for multiple Matr3 antibodies against different epitopes of the protein. Using these tools and conditions, we identified alterations in Matr3 levels and sub-cellular localization including aggregation in frontal cortex of FTD patients compared to non-neurological disease controls (NNDC).

**Functional Changes in Matrin 3 mutant neurons**: We performed initial experiments using an iPSC line generated from an ALS patient with the MATR3 F115C mutation. However, we subsequently determined that this patient derived line also contains a KIF5A intronic mutation[12], thus we cannot attribute phenotypes specifically to one gene defect or the other at this time. However the MATR3-F115C/KIF5A iPSCs and three healthy control iPSCs were differentiated into iPSC-MNs for 55 DIV using established protocols [13]. We performed Sholl analysis to measure changes in dendritic branching and measured spontaneous neuronal excitability of iPSC-MNs using a micro-electrode array (MEA) platform (Maestro, Axion Biosystems), using procedures and analytic tools we recently reported [14]. We detected significant decreases in dendritic complexity and increased excitability of MATR3-F115C/KIF5A iPSC-MNs across all age points when compared to controls (data not shown). Similar results of neuronal hyperexcitability have been shown in mouse models of ALS and patient iPSC derived MNs [15,16].

**Proposed One-Year and Long-Term Outcomes:**

The successful completion of this proposal will help elucidate the role of a new potential molecular mechanisms in neurodegenerative dementias. At the end of this proposal we will have better defined the extent of matrin 3 pathologies in different regions in FTD and AD. This will allow us to better understand what pathological changes are happening to matrin 3 in disease. These studies are significant as they may provide valuable information about new pathways that could be targeted for the development of new therapeutic strategies.

**Year End Progress Summary:**

Results from our work have begun to elucidate the how prevalent matrin 3 pathology is across neurodegenerative diseases. We performed pathological analysis across different disorders (mild cognitive impairment, AD, FTD, and ALS), and have found that matrin 3 pathology is relatively common occurrence across these disorders and correlates with severity of disease. Further, we have validated these findings using a different antibodies, demonstrating that it is not just an artifact of a specific antibody. We have found that in frontal cortex we can observe increased cytoplasmic mislocalization of matrin 3, loss of nuclear matrin 3 staining, and large aggregates within pyramidal neurons. These pathologies seem to be specific to certain layers of the cortex (e.g. layers 3 and 5), and have not previously been described in neurodegenerative diseases such as AD or FTD without matrin 3 mutations. This suggests cellular specificity and mechanisms involved in matrin 3 pathology. Further, our data is suggesting correlative trends with clinical features of dementia such as visuospatial memory, and pathological features such as Braak staging. In addition, we have found that matrin 3 also is present in other regions of the brain including the entorhinal cortex. We have also demonstrated that matrin 3 pathology frequently colocalizes with phosphorylated tau, and that neurons with high levels of phosphorylated tau have nuclear loss of matrin 3 staining. These findings are especially interesting, as they may suggest a mechanism in which increasing phosphor-tau deposition may lead to matrin 3 dysfunction, via mislocalization.

In addition, using in vitro models, we have demonstrated that matrin 3 is indeed sensitive to exogenous stressors. We have applied excito-toxic, oxidative, and inflammatory stressors and have found that matrin 3 is mislocalized or lost in response to stressors. We hypothesize that matrin 3 will also be vulnerable to dementia related stressors such as Aβ stimulation, and tau accumulation. We will continue *in vitro* approaches to dissect the mechanisms connecting matrin 3 dysfunction and dementia pathologies.

Together these findings have provided preliminary answers to our questions: Is matrin 3 pathology a common feature in dementias?; Is it associated to disease progression?; Is matrin 3 sensitive to neurodegenerative stressors?. These preliminary results will be the basis of RO1 and DOD grant applications that will be submitted this year. In addition, this work has also further developed and will continue in collaboration with new investigators such as Dr. Elliot Mufson, Dr. Sylvia Perez (AD co-pathology analysis), and Tgen (proteomics collaboration). While we have had some delays in optimizing technical aspects of the studies (e.g. image quantification, and neuronal cultures), we have worked to overcome these technical issues and optimized protocols. Further, we are in the process of preparing 2 manuscripts describing findings from these studies.

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Profiling Frontal Cortex White Matter APOE Astrocytes in Alzheimer's Disease.** Elliott Mufson, PhD, Marta Moreno, PhD, Sylvia Perez, PhD, Paul Coleman, PhD, Rita Sattler, PhD, Michael Malek-Ahmadi, PhD, Marwan Sabbagh, MD, Thomas Beach, MD, Christy Kelley, PhD, Jeffrey Kordower, PhD. Barrow Neurological Institute; Arizona State University; Banner Alzheimer's Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

**Specific Aims:**

Aim 1: We will test the hypothesis that frontal cortex white matter APOE positive astrocyte number and intensity are greater in APOEε4-carriers compared to non-carriers during the progression of AD. The findings will be correlated with case demographics, cognitive performance and neuropathological criteria.

Aim 2: We will test the hypothesis that frontal cortex white matter APOE positive astrocytes display greater alterations in the expression of genes related to myelin metabolism, inflammation and axon maintenance in APOEε4 carriers compared to non-carriers in preclinical stages of AD. These findings will be correlated with case demographics, cognitive scores, neuropathological data and with the findings from Aim 1.

**Background and Significance:**

APOEε4 is associated with increased amyloid-β deposition, tau aggregation and enhanced cognitive deterioration, however, the mechanisms by which APOEε4 mediates these effects are not fully understood. In the central nervous system, APOE is produced mainly by astrocytes, consequently APOEε4 genotype alters normal astrocyte function, potentially contributing to the risk for AD. APOE is a glycoprotein responsible for the maintenance of lipid levels in brain, mediating lipid transport between cell types. Pluripotent stem cell (iPS) derived APOEε4 astrocytes induce an accumulation of unsaturated triglycerides and lipid droplets, possibly reducing lipids. A recent study showed that reduced myelination in APOEε4 carriers is related to lipid dysregulation. Myelin changes are also present in healthy and asymptomatic individuals carrying ε4, suggesting a key role for APOE in myelin metabolism. It is known that axonal dysfunction contributes to cognitive decline in the frontal cortex a hub of the default mode memory network. Although we previously found an association between FC white matter (WM) astrocytic inflammatory markers and early memory deficits in AD, subject selection was not based on APOE genotype. In this proposal we will further investigate the cellular and molecular mechanism involved in APOE WM astrocytic dysfunction and cognitive deterioration in APOEε4 carriers.

**Preliminary Data, Experimental Design and Methods:**

**Preliminary data** showed the number and intensity of APOE in WM astrocytes of APOEε4-carriers vs non-carriers were compared, both increased in mild cognitive impairment (MCI) and in mild AD (mAD) groups, suggesting that APOEε4 astrocytes already display a hypertrophic phenotype in a prodromal stage of AD. In addition, a greater decline in episodic memory and global cognition were found between subject carriers versus non-carriers in the mAD group, reflecting a genotype effect on memory impairment. Finally, we found a negative correlation between episodic memory and intensity of astrocytes with immunoreactive for APOE. These preliminary findings suggest that FC WM APOEε4 astrocytes contribute to cognitive deterioration in AD. We investigated the following Aims:

**Specific Aim 1:** We will test the hypothesis that frontal cortex white matter APOE positive astrocyte number and intensity are greater in APOEε4-carriers compared to non-carriers during the progression of AD. **Experimental procedures: *Immunohistochemistry*:** FC sections will be singly stained with antibodies against APOE. Sections from all groups will be stained at the same time to avoid batch-to-batch variation and increases scientific rigor. ***Densitometric and area measurements*** will be performed using the Image J densitometry software.

**Specific Aim 2:** We will test the hypothesis that frontal cortex white matter APOE positive astrocytes display greater alterations in classes of genes related to myelin metabolism, inflammation and axon maintenance in APOEε4 carriers compared to non-carriers in preclinical stages of AD. **Experimental procedures:** Single population expression profiling combined with ***custom-designed microarray analysis*** applied to tissue from Aim 1.

**Proposed One-Year and Long-Term Outcomes:**

Year 1 Outcomes: During the current year of support, we completed Aim 1 and are currently in the process of finalizing a manuscript for publication.

Long-Term Outcomes*:* Although single cell RNA expression studies are time consuming and expensive over the long-term, we will continue to pursue Aim 2.

**Year End Progress Summary:**

**1.** We successfully completed a combined immunohistochemical quantitative analysis of APOE-positive astrocytes in frontal cortex (FC) white matter (WM) from individuals that came to autopsy with a premortem clinical diagnosis of no cognitive impairment (NCI), mild cognitive impairment (MCI), and mild to moderate AD. **Key findings:** 1. We found a significant increase in APOE-positive astrocytes in APOEε4 carriers compared to non-carriers in prodromal AD. 2. A decrease in Olig2-positive cells and myelin basic protein (MBP) optical density (OD) values in the WM of MCI APOEε4 carriers compared to non-carriers. 3. Luxol fast blue (LFB) OD values, which quantify total lipids, were higher in NCI APOEε4 carriers compared to both NCI non-carriers and AD carriers. 3. Positive correlations were found between LFB OD values and Olig2-positive cell counts with cognitive performance in APOEε4 carriers, but not non-carriers. In addition, we also published an article entitled ***"***Frontal cortex lipid alterations during the onset of Alzheimer's disease" linking lipid dysfunction in the frontal cortex to AD (Moreno et al., 2024). **Challenges:** We overcame methodological caveats related to the staining of Olig2 in human white matter.

**2.** The single-cell gene-array studies are ongoing. We predict that in prodromal AD, APOEε4 astrocytes of FC white matter will display classes of dysregulated genes related to myelination, inflammation, axonal energetic and lipids compared to non APOEε4 astrocytes. **Challenges:** We will likely need to generate additional funds to complete this Aim.

The findings derived from these studies will be used to submit an NIH R21 application.

**Future Grant Applications:** P01 AG014449 Competitive Renewal: Neurobiology of mild cognitive impairment in the elderly years 27-32.

# ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Deciphering the Resilience of the Brain Default Mode Network in Superagers.** Sylvia E. Perez, PhD, Elliott Mufson, PhD. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

**Specific Aims:**

Aim 1: We hypothesize that FC layer V-VI pyramidal neurons will display a greater number of mitochondria in Superagers (SA) compared to age-matched healthy (AHC) and mild-cognitive impairment (MCI) subjects using immunohistochemistry, immunoblot and densitometry techniques. Data will be correlated with demographic, cognitive performance, and neuropathological criteria.

Aim 2: We hypothesize that FC layer V-VI pyramidal neurons will display an upregulation of the expression of mitochondrial function, cell survival and metabolism and a downregulation of oxidative stress transcripts in SA compared to AHC and MCI. We will use qPCR to validate differentially regulated genes.

**Background and Significance:**

While normal aging is associated with a cognitive decline, there is an exceptional group of people 80 years or older designated SA whose episodic memory is superior to age-matched peers and comparable to individuals 20 to 30 years younger. However, the factors that contribute to the preservation of memory in the SA phenotype are poorly understood to those associated with components of the default mode network (DMN) (cingulate cortex, precuneus, prefrontal cortex). In SA, this connectome, key in episodic memory performance, displays larger cortical volumes, stronger connectivity and preserved functionality compared to AHC. Numbers of amyloid plaques and neurofibrillary tangles in SA varied in DMN compared to aged-matched controls. Together these findings suggest that the DMN in SA has a greater brain resilience independent of Aβ and tangle pathology. Therefore, it is imperative to determine the cellular and molecular mechanism(s) underlying neuronal resilience in these extraordinary elderly populations within the DMN.

**Preliminary Data, Experimental Design and Methods:**

Preliminary RNA sequencing (RNA seq) profiling in the frontal cortex (FC) demonstrated a significant upregulation of the two subunits of the mitochondrial ATP synthase, mitochondrial ATP Synthase Membrane Subunit 6 (MT-ATP6) and 8 (MT-ATP8) compared to AHC. Both mitochondrial transcripts showed a strong positive correlation with cognitive status using the mini-mental state examination (MMSE) test. Amazingly, immunohistochemistry revealed a greater accumulation of mitochondria in cytoplasmic FC layers V and VI pyramidal neurons in SA compared to AHC. This increase in mitochondria occurred despite comparable Aβ load between SA and AHC, however, tangle pathology was absent in both groups.

**Specific Aim 1: Mitochondrial upregulation:** We will test the hypothesis that FC pyramidal neurons in layers V and VI will display a greater number and size of mitochondria in SA compared to AHC and MCI. **Experimental procedures: *Immunohistochemistry*:** FC sections will be singly stained with antibodies against mitochondria. Sections from all groups will be stained at the same time using the same chemical reagents to avoid batch-to-batch variations, which increases scientific rigor. ***Densitometric and area measurements:*** Quantification of the relative optical density (OD) of mitochondria positive neurons will be performed using the Image J densitometry software program as we reported. ***Quantitative immunoblotting****:* Cortical quantitative immunoblotting using frozen tissue, free of white matter, will be performed, protein signals normalized to β-tubulin and analyzed in three independent experiments.

**Specific Aim 1: Mitochondrial upregulation:** We will test the hypothesis that FC pyramidal neurons in layers V and VI will display a greater number and size of mitochondria in SA compared to AHC and MCI. ***Expected Outcomes and Interpretations:*** We predict higher numbers and increase size of mitochondria in the FC in SA followed by AHC and MCI, reflecting greater neuronal resilience conferred by the mitochondria in SA.

**Specific Aim 2: Single neuronal population mRNA expression in FC:** We will test the hypothesis FC neurons in layers V and VI in SA will display a greater upregulation of classes of genes related mitochondrial function, cell metabolism, cell signaling, cell survival and downregulation of oxidative stress genes in SA compared to AHC and MCI cases. **Experimental procedures:** Single population expression profiling combined with ***custom-designed microarray analysis*** will be applied to tissue from Aim 1 according to our published protocols.

**Proposed One-Year and Long-Term Outcomes:**

***Aim 1: Expected Outcomes and Interpretations:*** We predict higher numbers and increase size of mitochondria in the FC in SA followed by AHC and MCI, reflecting greater neuronal resilience conferred by the mitochondria in SA.

***Aim 2: Expected Outcomes:*** We provide novel insight into the molecular signature of FC neurons 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 reflecting of a greater energetic power and more efficient cellular metabolism needed to challenge the ravages of aging and disease onset compared to AHC and MCI.

**Year End Progress Summary:**

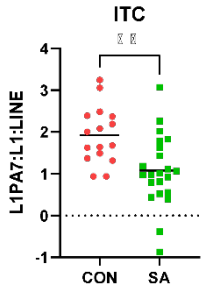
***Aim 1:*** **We predict higher numbers and increase size of mitochondria in the FC in SA followed by AHC and MCI, reflecting greater neuronal resilience conferred by the mitochondria in SA.**

**Immunohistochemistry combined with densitometry.** DMN cortical areas, frontal cortex (FC), posterior cingulate (PCC), precuneus (PreC) and inferior temporal cortex (ITC) sections from 18 SA and 18 AHC subjects were immunostained using several mitochondrial markers. Optical density (OD) was performed and analyzed in pyramidal neurons containing mitochondrial immunostaining in layers V-VI in SA vs AHC in these DMN hubs. OD preliminary data demonstrated that SA have higher numbers of mitochondria in the pyramidal neurons across the DMN cortical areas. Interestingly, the values of OD mitochondrial immunostaining correlated significantly with episodic memory and global cognitive scores in SA, but not in AHC. This data suggests that neuronal mitochondrial content in DMN is associated with better cognitive performance, at least in SA. We are using another mitochondrial marker, TOMM-40, to evaluate neuronal mitochondria numbers in the DMN.

**Quantitative immunoblotting** showed upregulation of proteins associated with mitochondrial biogenesis. Protein levels of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), that stimulates mitochondrial biogenesis, and nuclear respiratory factor 1 (NRF1), a regulator of mitochondrial biogenesis, were significantly higher in SA compared to AHC (controls, CON) in the frontal cortex (FC) and posterior cingulate cortex (PCC), suggesting that upregulation of mitochondrial biogenesis pathway underlies the higher numbers of mitochondria in SA. In fact, more mitochondria, more ATP, and energy availability in the cells to overcome the ravaging effects of aging (oxidative stress and AD pathology) in a more efficient manner, that translates in greater cognitive performance in SA compared to AHC.

***Aim 2:*** **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.**

This aim using single cell gene-array is still ongoing. However, RNA sequencing was performed in the inferior temporal cortex (ITC) in SA and AHC. Preliminary analysis showed a differential transcript expression of mitochondrial classes of genes between SA and AHC, supporting the concept of mitochondria as a key player in cognitive performance in SA. In addition we found a significant decrease in gene expression in several transposable elements (for example: L1PA7:L1:LINE) in SA compared to AHC in the ITC. Transposable RNA expression correlated significantly with episodic memory and global cognitive scores in SA (see below), but not in AHC. Transposable elements become deleteriously activated with age and associated with tau pathology and cognitive decline in the Alzheimer's disease context. Therefore, this preliminary data suggests that lower expression of the transposable elements in SA are associated with better cognitive function.




This preliminary data will be used to apply for federal (NIH R01 or R21) and private foundation (Alzheimer's association) support.

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Hispanic Enrollment in Alzheimer's Research Trials (The H.E.A.R.T. Program at BNI).**
Marwan Sabbagh, MD, Amy McLean FNP, Anna D. Burke, MD, Krista Hanson PhD. Barrow Neurological Institute; 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 the 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 identify and mitigate against cultural barriers limiting access for Hispanic patients to enroll into Alzheimer's disease clinical trials.

**Background and Significance:**
Hispanics 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 75 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. Recruitment of an additional 15 new Hispanic enrollees in the next year to bring our site total to 25 participants who identify as Hispanic/Latino.

2. Retention of existing Hispanic enrollees.

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. Continue to push for further growth in the number of bilingual staff members within the Cognitive Research Program at BNI and support the cost of those staff members becoming certified medical translators.

**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 is designed to increase recruitment and retention of Hispanic subjects in the Arizona Alzheimer's Disease Research Center (ADRC) and other research protocols by removing unique cultural barriers and increasing awareness and access to meet the defined program goals.

1. As with the prior funding period, over the course of the 2023-2024 project period, BNI successfully retained all existing bilingual team members, including the full-time bilingual research psychometrist, despite the uncharacteristically high staff turnover rates that were experienced throughout the field of research as a whole. The retention of our entire 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. Two of our team members, Angelica Garcia and Jalisa Santiago, attended the 4$^{th}$ annual Latinos & Alzheimer's Symposium hosted in San Diego by the Alzheimer's Association. In attending the symposium, Angie and Jalisa gained valuable insight into the barriers to research participation that many Hispanic patients experience and learned best practices for overcoming many of those barriers.

3. The BNI research team worked closely with members of our outreach office to identify and attend multiple outreach events that catered exclusively to the Hispanic community.

4. Barrow staff worked relentlessly to maintain existing relationships with Hispanic study participants while also enhancing the site's ability to communicate meaningfully with the Hispanic community. As part of this effort, all bilingual staff members have been trained to conduct the Clinical Dementia Rating Scale (CDR) in Spanish and maintained that certification. This greatly expands our ability to administer scales for the ADRC project to participants whose preferred language is Spanish.

5. Margeaux Snell, the BNI Research Program Manager, and Jalisa Santiago, one of BNI's bilingual research coordinators, attended the AAIC Advancements: Toward Health Equity in Alzheimer's Disease and Related Dementias meeting in San Antonio, TX in fall 2023. This conference explored inequities in prevention, diagnosis and treatment of Alzheimer's and related dementias. Specifically, this conference focused on reaching more diverse populations and

educating on the various behavioral, biological, environmental and sociocultural factors that impact access to care and willingness to participate in research.

6. All Spanish-speaking research coordinators and psychometrists at BNI have been trained to conduct the Montreal Cognitive Assessment, or MoCA, in Spanish. This will be crucial as we prepare to hold our first ever Spanish language only Memory Screening event in July 2024.

7. All ADRD trials being conducted at Barrow now 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.

8. Currently, 25% of all participants enrolled in the ADRC study at Barrow identify as being of Hispanic or Latino ethnicity. Of the 40 participants enrolled at the BNI site this funding period, 10 have indicated that they identify as Hispanic/Latino.

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Detection of Alpha-Synuclein in Neurodegenerative Diseases.** Marwan Noel Sabbagh, MD, Giovanni Malaty, MD, Holly Shill, MD, Boris DeCourt, PhD. Barrow Neurological Institute; Texas Tech University; Arizona Alzheimer's Consortium.

**Specific Aims:**

To assess the validity of detection and quantification of alpha synuclein in cohorts of neurodegenerative diseases**. Hypothesis:** *a-syn is detectable in plasma and will correlate with alpha synuclein in central nervous system (CNS) tissues***. Expected outcomes:** We aim to utilize IMR assays to assess the diagnostic utility of, p-Tau-181, and α-synuclein in identifying and differentiating cases of PDD (n=5)/ DLB (n=5) when compared to, PD without dementia (n=10) and AD (as a disease control, n=10). Quantification of plasma levels of these biomarkers will be compared to CSF, saliva and nasal swab all gathered at the same time on the same cohort to evaluate potential opportunities for optimizing sensitivity and specificity of these biomarkers, all with the intention of advancing clinical methodologies used in clinical differentiation and diagnosis. This is a cross-sectional study to be completed within one year to provide pilot data for an NIH R21.

**Background and Significance:**

Given the wide clinical overlap that exists between Dementia with Lewy Bodies (DLB), Parkinson's dementia (PDD) subtypes, the arbitrary clinical criteria currently employed to differentiate them, and the overall paucity of reliable diagnostic assays available for differentiation, there would be tremendous value for biomarker screening in plasma and/or saliva. Plasma collection is less invasive, more cost-effective, and more accessible than cerebrospinal fluid (CSF) testing. The utility of plasma biomarkers for the diagnosis of PDD and DLB has been hampered by issues of both assay sensitivity/specificity, as well as low detection thresholds, as concentrations of pathologic components in the plasma fall precipitously when compared to CSF, most notably seen in traditional enzyme-linked immunosorbent assay (ELISA) platforms.

Antigen-targeting detection assays including single molecule assay (SIMOA), multimer detection system (MDS), immunoprecipitation/mass spectrometry (IP/MS), and immunomagnetic reduction (IMR) have increased sensitive quantification of plasma biomarkers (Janelizde 2021, Thissen 2021, Chong 202137-42). Other platforms (mass spec, SIMOA, ELISA) have not fully developed a reliable assay to detect α-synuclein. ImmunoMagnetic Reduction (IMR) is of particular interest for our study goals as it can detect α-syn. IMR employs nanobead-conjugated antibodies which bind to specific target analytes. Using a superconducting quantum interference device (SQUID) and alternating current (AC) magnetosusceptometer, recording resultant differentials in measured magnetic signal during this binding allows for the ultrasensitive measurement of plasma concentrations of classic neurodegenerative biomarkers such as tau and Aβ42 with exceptional accuracy (35, 43-44). IMR has been clinically validated and approved for the diagnosis of AD by the Taiwanese FDA and has shown to have superior accuracy when compared to other plasma detection media such as ELISA and CLIA (45).

**Preliminary Data, Experimental Design and Methods:**

**Experimental Designs and Methods:** The total sample size will be 30 subjects including 10 AD [McKhann 2011], 10 PD without dementia [Hughes criteria] and 10 DLB/PDD [McKeith criteria, Hughes Criteria for PD and DSM5 for major neurocognitive disorder]. The I/E criteria include being able to undergo test procedures and meeting the diagnostic criteria. The variables to be collected include age, education, gender, MOCA, FAST, AQ, UPDRS, and H-Y stage.

**Preparation of plasma samples**
Plasma biomarkers (t-tau, p-tau, Ab42, alpha-syn) will be assayed by ImmunoMagnetic Reduction (IMR) technology (MagQu, Inc).

Non-fasting plasma samples were collected in EDTA-coated vacutainers (Becton Dickinson, New Jersey) followed by centrifugation with speed ranges from 1500-2500 g for 15 minutes at room temperature. The upper layer (plasma) was transferred to a new 15-ml tube, aliquoted into 1.5 ml tubes, and stored at -70 ˚C or lower. Sample aliquots were shipped on dry ice to MagQu Co., Ltd. for IMR assays. Assays were performed without the knowledge of demographic features and clinical diagnosis of the subjects.

**Assays of Aβ40, Aβ42 and t-Tau in human plasma**
Before assay, frozen aliquoted samples will be thawed on ice. Sample preparation and assay were all performed at room temperature. Assays were performed in duplicate from each sample, respectively for Aβ40, Aβ42, and t-Tau, pTau181. The volumes of the reagents and plasma samples were 80-µl reagent (MF-AB0-0060, MagQu) and 40-µl plasma for Aβ40 assay; 60-µl reagent (MF-AB2-0060, MagQu) and 60-µl plasma for Aβ42 assay, 80−µl reagent (MF-TAU-0060, MagQu) and 40-µl plasma for t-Tau assay, and 80−µl reagent (MF-PT1-0060, MagQu) and 40-µl plasma for pTau181 assay. Samples and reagents are mixed briefly in the special-sized glass tubes and sealed. The tubes are then placed inside the sample channels of the IMR analyzer (XacPro-S, MagQu) for assay. The concentrations of Aβ40, Aβ42, t-Tau or pTau181 were calculated according to the standard curves respective to each marker. The means of the values obtained from duplicate measurement were calculated for each marker and each sample.

*Saliva*. We will collect saliva in customized tubes containing a blend of dry protein stabilizers developed by our strategic partner Oasis Diagnostics Corporation. Within 24h to 7 days, the specimens are centrifuged, aliquoted into cryogenic tubes, and stored at -80ºC. Frozen saliva samples are shipped by PI #2 to Oasis Diagnostics Corporation for biomarker assessments in a blind manner. Analytes tested include Aβ40, Aβ42, total tau, P-tau-181, α-Syn, NfL. The saliva markers will be compared to the levels of the same markers in plasma and CSF.

*CSF*. After consent, patient will be prepped and draped in the usual sterile fashion placed upright. The L3 interspace will be palpated and marked. 5cc of 1% lidocaine will be injected subcutaneously and percutanously. A 25 gauge 90mm Sprotte needle with introducer will cannulate the dura. The first 2 cc wlll by sent for the Syntap Test. An additional 2cc will be sent for Aβ42 and ptau 181 (MagQu-IMR)

**Statistical analysis**
Parametric comparison of means was performed by One-Way Analysis of Variance (ANOVA). Sample means and deviations were then compared by Student-Newman-Keuls or Kruskal-Wallis testing for pairwise analysis to further test sample means for significance. Spearman's correlations were performed to determine the correlations of the levels of single plasma biomarkers, their composite biomarker products, and several demographic features.

**Proposed One-Year and Long-Term Outcomes:**
We will complete comparative analyses of alpha synuclein in CSF (MaqQu quantitative, Amprion SynTap) vs plasma alpha synuclein. Nasal swabs are an exploratory aim. If successful, we will pursue an R21 to perform a larger validation study.

**Year End Progress Summary:**
Throughout the past year, we have made significant strides in our ongoing research endeavor. We were notified of the award on July 1, 2023 and promptly submitted the IRB application in July 30, 2023. Despite encountering some delays related to contracting arrangements of subawards

and samples, we received IRB approval in February 2024 enabling us to initiate study enrollment that same month. To date, we have successfully enrolled 19 participants, with a target of 30, including participants diagnosed with mild cognitive impairment/Alzheimer's Disease, Parkinson's Disease and Dementia with Lewy Bodies**.** Moving forward our plan after July 1, 2024 encompasses a multi faceted approach**:**

- This includes analysis of biomarker data
- drafting a manuscript of the results for scholarly journal submission,
- dissemination of our findings at the Arizona Alzheimer's Association International Conference ( AAIC) in 2025 and
- the submission of an R21 grant proposal in 2025.

Our plan underscores our commitment to scientific rigor and exemplifies our dedication to advancing knowledge and addressing critical challenges in the field of neurodegenerative diseases.

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Generation of Induced Pluripotent Stem Cells (iPSC) from LBD Patients and Temporal Characterization of iPSC-Differentiated Neurons.** Rita Sattler, PhD (PI), Anna Burke, MD (co-PI), Marwan Sabbagh, MD (co-PI), Patrick Pirrotte, PhD, Ignazio Piras, PhD, Thomas Beach, MD, Geidy Serrano, PhD, Ileana Lorenzini, PhD. Barrow Neurological Institute; Translational Genomics Research Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

**Specific Aims:**

***Specific Aim 1. Isolation of LBD patient peripheral blood mononuclear cells (PBMCs) and generation of iPSCs.*** We will enroll PDD and DLB patients with confirmed diagnosis to provide us with blood samples, which will then be utilized to isolate PBMCs. PBMCs will be cultured and quality controlled before submitting for iPSC reprogramming using the services of the Cedars Sinai Stem Cell Core facility, which we have employed for several years for reprogramming purposes.

***Specific Aim 2: Phenotypic examination of LBD patient derived iPSC-neurons.*** iPSCs from PDD and DLB patients will be differentiated into iPSC cortical forebrain neurons and at multiple time points during differentiation will be examined for a-synuclein inclusions, phosphorylated tau, the presence of amyloidogenic Ab peptides as well as cytoplasmic inclusions of TDP-43. In addition, we will examine synaptic dysfunction by quantifying number of synapses, evaluating dendritic morphologies and measuring neuronal excitability using a multi-electrode array system (MEA). Finally, we will determine if PDD and DLB iPSC cortical neurons are more susceptible to cellular stressors.

**Background and Significance:**

***Lewy Body Dementia (LBD).*** Lew body dementia (LBD) is often referred to as an umbrella term for two disorders sharing clinical and pathological features: Parkinson's disease with dementia (PDD) and dementia with Lewy Bodies (DLB). While PD is typically thought of as a motor disorder, there are significant non-motor symptoms that are often deemed by patients, to be equally damaging to quality of life. A common and devastating non-motor symptom of PD is dementia. Patients who have PD are 2-6 times more likely to get dementia than their age-matched healthy peers, and approximately 50-80% of PD subjects progress to PD with dementia (PDD) within 10 years of diagnosis. DLB is a closely related synucleinopathy with substantia nigra dopaminergic loss (like PD and PDD) that manifests with dementia first and then with motor parkinsonism. Typically, subjects with DLB have dementia before or at the same time as PD motor symptoms start, and get worse over time, while PDD subjects develop cognitive dysfunction after many years of motor PD. The temporal occurrence of dementia onset is thought to be the major distinction between PDD and DLB. The co-existence of dementia as a destructive non-motor symptom leads to a loss of independence, the requirement for more significant care, depression, and increased mortality in this patient population, emphasizing the need to better understand the specific disease mechanisms of this dementia spectrum disease.

***IPSC models of LBD.*** Neurodegenerative diseases are now routinely modeled by means of human patient-derived cell culture systems generated using induced pluripotent stem cell (iPSCs). And while PD, AD and frontotemporal dementia (FTD) have been extensively studied using patient-derived iPSC differentiated into neurons and glial cells, including reports from our laboratories, no studies have been published to evaluate disease pathogenesis and, most importantly, the temporal progression of synucleinopathy and dementia in PDD and DLB patient-derived human cell culture models.

**Preliminary Data, Experimental Design and Methods:**
The Sattler laboratory has extensive expertise in iPSC culture modeling and has established and validated the generation of patient-derived iPSC differentiated neurons, astrocytes and microglia. Drs. Burke and Sabbagh provide care to large numbers of LBD patients at the BNI Alzheimer's and Memory Disorders Clinic and can therefore provide LBD patient plasma to be used for the proposed studies.

***Specific Aim 1***
***(1A) Patient recruitment***. LBD patients (PDD and DLB) will be recruited at the BNI Alzheimer's and Memory Disorders Clinic for a blood donation with the purpose of generation iPSCs from the isolated PBMCs. (>5 DLB, >5 PDD and >5 healthy control subjects; up to 30 total) will be included in the study. ***(1B) Isolation of PBMCs.*** Blood collected in Vacutainer tubes will be processed for PBMC isolation via sequential centrifugation steps of blood plasma/PBMC layer. After the final centrifugation step, PBMC pellet will be frozen and stored at -80C. ***(1C) Reprogramming into iPSCs***. 6 (3 PDD, 3 DLB) of the <30 proposed patient PBMC lines will be reprogrammed using the services of the Cedars Sinai Stem Cell Core facility. The remaining PBMCs will be banked for future iPSC reprogramming purposes.

***Specific Aim 2***
PDD and DLB iPSC-CNs, in addition to 3 healthy non-neurological controls, will be analyzed at different maturation time points for α-synuclein inclusions and Lewy-Body neurites. In addition, cells will be analyzed for dementia-related pathologies, including phosphorylated tau, the presence of Aβ as well as cytoplasmic inclusions of TDP-43. Finally, we will evaluate synaptic dysfunction and neuronal susceptibility to cellular stressors. *These data will provide novel temporal information on PD and dementia disease phenotype development and manifestation in PDD and DLB iPSC-CNs.*

***(2A) Measurements of PD disease pathology.*** iPSC-CNs will be immunostained for overall levels of α-synuclein, as well Ser129-phosphorylated α-synuclein.

***(2B) Measurements of AD disease pathology.*** iPSC-CNs will be immunostained for amyloid and Tau. Given the recent indication of the presence of TDP-43 cytoplasmic inclusions in subsets of AD patients, we will immunostain for TDP-43 using anti-TDP43 and anti-pTDP-43 antibodies.

***(2C) Neuronal synapse numbers.*** To measure and quantify the number of remaining functional synapses per dendritic length, hiPSC-CNs will be co-labeled for PSD-95 and SV2, a post- and pre-synaptic marker protein, respectively.

***(2D) Morphological characterization of neuronal dendrites and spines.*** Alterations in dendritic morphologies have been observed in many neurodegenerative diseases and dementias. To study dendrite and spine morphology, hiPSC-CN will be transduced with a lentivirus expressing eGFP at low multiplicity followed by analyses for spine density, dendritic branching and length as shown previously.

***(2E) MEA measurements.*** iPSC-CNs 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 three times a week between 30 to 75 div. Electrical activity will be analyzed using Axis 2.0 software.

***(2F) Vulnerability to glutamate excitotoxicity.*** iPSC neurons from derived from varying neurodegenerative disease patients have been shown to exhibit increased vulnerability to cellular stressors including glutamate excitotoxicity and neurotrophic factor withdrawal. We will test whether PDD and DLB iPSC cortical neurons show similar susceptibility and if yes, whether this susceptibility differs between the two diseases.

**Proposed One-Year and Long-Term Outcomes:**
These exploratory studies will enable us to evaluate the temporal progression of DLB vs PDD using patient derived iPSC-cortical neurons. 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 perform multi-omics analyses on iPSC-neurons, but also glial cells in addition to performing snRNA seq analyses from postmortem brain tissues of DLB and PDD patients.

**Year End Progress Summary:**
***Completed aspects of our studies:***
*Specific Aim 1*
*Recruitment of LBD patients, collection of PBMCs and reprogramming into iPSCs.*
We have successfully enrolled 8 participants for the PBMC collection (4 patients (3 DLB, 1 PDD); 4 healthy controls). Of these 8 PBMC samples, we submitted 3 for preprogramming using the services at Cedar Sinai's Stem Cell core facility. These lines are being generated at we speak, and we should receive fully quality controlled iPSCs within the next 6 weeks. The remaining PBMCs are stored at -80C.

*Specific Aim 2*
*Differentiation of iPSCs into cortical neurons and neuronal phenotypic characterizations.*
Fortunately, the Sattler lab was able to obtain previously reprogrammed DLB iPSC lines through collaborative efforts. To optimize the neuronal phenotypic analyses, 2 DLB, 1 PDD, 3 HC iPSC lines have been differentiated into iPSC-cortical neurons and are currently analyzed for: PD and AD proteinopathies and synaptic changes (***2A, B, C, D***). A new differentiation has been started to be utilized for measurements of neuronal firing (***2E***).

***To be completed:***
*Specific Aim 1*
LBD patient, especially PDD patient, enrollment is still ongoing to be able to increase the number of PDD patient lines to at least 3, and hopefully reach at least 5 participants for each experimental group. Once we have the additional PBMCs collected, we will send at least two more PDD samples for reprogramming to Cedars Sinai.

*Specific Aim 2*
We will repeat phenotypic neuronal analyses from the newly differentiated iPSC lines to increase the number of patient lines evaluated for temporal cellular and molecular changes of AD and PD, with the goal of establishing patient subgroup specific dysfunctions, which might help with the development of early biomarkers to identity and distinguish subtype-specific patients in the clinic at early stages of clinical symptoms.

***Challenges***
Our biggest challenges lied in timely recruitment of patients. LBD is not a common neurodegenerative disease like Alzheimer's disease, and in particular, recruitment of PDD patient seems more difficult. With the additional support from our PD clinic, we were finally able to recruit our first PDD patient and are hoping to additional ones to add to our sample collection.

***Future grant applications***
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 perform multi-omics analyses on iPSC-neurons, but also glial cells in addition to performing snRNA seq analyses from postmortem brain tissues of DLB and PDD patients.

# CRITICAL PATH INSTITUTE
# PROJECT PROGRESS REPORT

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Harmonizing Tau PET in Alzheimer's Disease: the CenTauR Scale and the Joint Propagation Model.** Antoine Leuzy, PhD, Diane Stephenson, PhD, Yashmin Karten, PhD, Members of the Critical Path for Alzheimer's Disease Consortium. Critical Path for Alzheimer's Disease Consortium, Critical Path Institute; Arizona Alzheimer's Consortium.

**Specific Aims:**

The grant will focus on the following objectives: 1) Compare the Joint Propagation Model (JPM) with other approaches, including a machine learning-based method that are currently being implemented in the Head-to-Head Harmonization of Tau Tracers in Alzheimer's Disease (HEAD) study. In this multi-site trial, [18F]flortaucipir and [18F]MK-6240 will be compared head-to-head at baseline and longitudinally in approximately 600 individuals across the AD clinical continuum; 2) Assessment of the JPM in mesial temporal subregions known to be affected by early tau pathology. While strongly correlated in cortical regions, previous head-to-head studies comparing [18F]flortaucipir and [18F]RO9483 and [18F]GTP1 with [18F]PI-2620 and [18F]MK-62402 have shown modest correlations in the hippocampus, most likely due to choroid plexus uptake.

**Background and Significance**:

The CPAD consortium has re-prioritized its goals and objectives, based on member consensus, to prioritize tau positron emission tomography (PET) harmonization efforts. Building on the success of amyloid PET, the past decade has seen rapid progress in the development of tau-specific PET tracers, including: [18F]flortaucipir—approved by the U.S. Food and Drug Administration to aid in the diagnosis of AD—[18F]RO948, [18F]MK-6240, [18F]GTP1, [18F]PI-2620, and [18F]florzolotau. As a result, tau PET is increasingly used in the clinical research evaluation of patients and as both a predictive and response biomarker in AD clinical trials evaluating disease-modifying therapies. However, the tracers differ in their degree of specific and nonspecific binding, have different regional off-target retention, or have not yet been fully characterized, preventing them from being meaningfully compared or combined. It was in this context that a Working Group of experts across industry and academia led by the Critical Path Institute's (C-Path) CPAD was convened at the 2022 Alzheimer's Association International Conference (AAIC) to discuss standardization of quantitative tau PET imaging (the units of this scale are termed "CenTauRs").

The availability of a common scale for use with tau PET would facilitate:
1) direct comparison of results across labs even when different analysis methods or tracers are employed;
2) clear definition of cut-offs for the defining early tau pathology in cognitively unimpaired controls;
3) further definition of the range of tau pathology characteristic of AD;
4) more consistent representation of longitudinal change, including in clinical trials;
5) direct comparison of the characteristics of different tracers. Use of CenTauRs would also allow for the combination of results across large scale observational studies.

**Preliminary Data, Experimental Design and Methods:**

Initial analyses performed by the Working Group have focused on two methods. The first method involved adapting a linear regression-based approach developed for use amyloid PET. This method uses an arbitrary scale (the units of which are termed "Centiloids"), based on a reference

tracer ([11C]PIB, then and still accepted as the "gold-standard" among amyloid tracers) combined with a prescribed processing methodology and a linear transform that establishes 0 and 100 as the mean values of young Aβ-negative cognitively unimpaired (CU) individuals and typical AD dementia patients, respectively. The Working Group also tested a novel second method, termed the JPM, an approach that does not require the use of a reference tracer. The JPM is based on a statistical model that simultaneously models the relationships between data from anchor point subjects and data from subjects in multiple head-to-head studies and the CenTauR scale, providing mapping equations that allows for conversion from tracer specific standardized uptake value ratios (SUVR) to the CenTauR scale.

Thus far, a total of 117 individuals with head-to-head tau PET have been included from five cohorts: [18F]RO948 vs [18F]flortaucipir (BioFINDER-2, n=37), [18F]MK-6240 vs [18F]flortaucipir (University of Pittsburgh, n=15),11 [18F]GTP1 vs [18F]PI-2620 (Roche/Invicro, n=26), [18F]GTP1 vs [18F]MK-6240 (Roche/Invicro, n=22), and [18F]RO948 vs [18F]PI-2620 (Fundació ACE Healthy Brain Initiative (FACEHBI) study, n=17). Anchor point values were derived from an additional 333 individuals: [18F]flortaucipir (BioFINDER-2, n=53); [18F]GTP1 (Roche/Invicro, n=26); [18F]MK-6240 (AIBL, n=171); [18F]PI-2620 (Life Molecular Imaging, n=19); and [18F]RO948 (BioFINDER-2, n=64). Criteria for the CenTauR-0 group were CU individuals who were negative on both amyloid (visual read and Centiloids <10, a cutoff associated with the absence of Aβ plaques and tau PET (visual read). Criteria for the CTR-100 group were having a clinical diagnosis of AD dementia, age <75, MMSE >20 and being positive on both amyloid (visual read and Centiloids >50) and tau PET (visual read).

**Proposed One-Year and Long-Term Outcomes:**

Using head-to-head data from five different tau PET tracers, we developed a novel method (JPM) for harmonizing tau PET SUVR data to a common scale (CenTauRs). This method performed well in AD-specific ROIs covering areas showing early, intermediate and late tau NFT pathology. These results are summarized in a manuscript that is now in press in Alzheimer's & Dementia, with a second manuscript summarizing how to convert SUVR data to the CenTauR scale underway. Further work is required to explore the suitability of the JPM for use in medial temporal lobe subregions.

In terms of long-term outcomes, we aim to extend the cross-sectional work using the JPM to longitudinal tau PET. Preliminary work using longitudinal [18F]flortaucipir and [18F]MK-6240 shows that differences in dynamic range can be accounted when applying the model longitudinal data assuming a clinical trial that combines two or more tracers (e.g., when calculating the number of subjects needed per arm to reach 80% power to detect a treatment effect, assuming a 50%/50% mix of tracers, significantly fewer subjects were required when using sample weighting based on estimated differences in dynamic range).

**Year End Progress Summary:**

Using head-to-head data, strong linear associations (R2>0.90) were observed between tracers across cortical regions of interest. Comparison of the JPM with the linear regression approach showed that the JPM offers a more straightforward approach to tau PET harmonization. Further, the mapping equations from individual tracer SUVRs to the CenTauR scale were found to be more accurately estimated by the JPM compared to the linear regression approach using cross-fold validation (mean square prediction error). These results are summarized in a manuscript that is now in press in Alzheimer's & Dementia.

With the first portion of the CPAD-led tau PET harmonization work now completed, we are currently focused on a second manuscript describing how to convert SUVR data to the CenTauR scale using the JPM described in the Alzheimer's & Dementia paper. After consulting with the broader Working Group, this will entail making available tracer specific datasets (100 scans for [18F]flortaucipir, [18F]RO948, and [18F]MK-6240) publicly available on the Global Alzheimer's Association Interactive Network (GAAIN) website. After validating their processing pipeline by ensuring that calculated SUVR values are highly correlated with values centrally calculated at CPAD—using R2 and slope/intercept, same as for Centiloids—sites can proceed to convert their SUVR data to CenTauRs using equations that will be included in the manuscript.

The JPM model assumes different variances in the measurement error term across tracers, but structured in such a way that the signal-to-noise ratio is identical across tracers on the CenTauR scale. This assumption was motivated by the lack of structured data (e.g., test-retest data from individual tracers) that could enable simultaneously estimation of mapping equations to the CenTauR scale and individual tracer-specific variance parameters. CPAD is finalizing collection of test-retest data for the included tracers ([18F]flortaucipir,17 [18F]RO948, [18F]MK-6240, [18F]PI-262020 and [18F]GTP121) in order to test this assumption. While a federated analysis will be performed across the major tau PET datasets, preliminary findings indicate that the use of JPM-based CenTauRs results in more comparability across tracers, compared to SUVR.

The first objective was proposed following a series of discussions at different scientific meetings and via correspondence. We continue to seek access to the proposed HEAD study for comparisons once this dataset becomes available. With respect to the second aim, while strong linear correlations were observed within a composite medial temporal lobe ROI, more modest non-linear associations were apparent when examining associations within sub-regions, including the entorhinal cortex and hippocampus. It is necessary to use larger head-to-head datasets to investigate whether this is a problem that can be resolved by the JPM, and whether harmonization in these sub-regions can be achieved.

# MAYO CLINIC ARIZONA
# PROJECT PROGRESS REPORTS

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Targeting Both Amyloid-β and α-Synuclein in Alzheimer's Disease with AAV-Mediated Delivery of Bispecific Single-Domain Antibodies.** Zonghui Ding, PhD, John Fryer, PhD. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

**Specific Aims:**

**Aim 1**: To discover, produce, and validate sdAb clones against $A\beta_{(pE3-42)}$ and αSyn utilizing our recently established immune sdAb libraries.

**Aim 2**: To explore the effects of AAV-mediated delivery of bispecific sdAbs targeting both $A\beta_{(pE3-42)}$ and αSyn and their mechanisms of action in an AD mouse model with Lewy-related pathology.

**Background and Significance:**

Alzheimer's disease (AD) is the most common cause of dementia and is pathologically characterized by extracellular plaques formed by the deposition of amyloid-β (Aβ) peptide and intracellular tangles comprised of hyperphosphorylated forms of the tau protein. However, accumulating evidence suggests that the presynaptic protein α-synuclein (αSyn) is involved in the pathophysiology of AD. Lewy-related pathology, primarily composed of αSyn, is present in more than 50% of post-mortem AD brains, and high levels of αSyn are found in the cerebrospinal fluid (CSF) of patients with mild cognitive impairment (MCI) and AD. It has been reported that overexpression of mutant forms of Aβ, tau, and αSyn in a transgenic mouse model may promote the accumulation and aggregation of each other and promote cognitive dysfunction in humans. Furthermore, reducing αSyn expression in an AD mouse model rescued and reversed the AD pathology-induced neurodegenerative phenotype. Therefore, both Aβ and αSyn are increasingly attractive targets for immunotherapy in AD. FDA approved anti-amyloid antibody aducanumab for treatment of AD last year, despite a lot of controversies from the field. While most immunotherapies have been developed for Aβ and tested in AD, the field has progressed to targeting other proteins including αSyn. Single-domain antibodies (sdAbs) are increasingly considered as alternative to the traditional monoclonal antibodies (mAbs). The small size, stability to heat and pH extremes, low immunogenicity, and facility to express as multimers with enhanced activities, make sdAbs preferred therapeutic agents. Therefore, we hypothesize that targeting $A\beta_{(pE3-42)}$ and αSyn with anti-amyloid and anti-Syn sdAbs may serve as a potential therapeutic approach for AD. The success of development of novel sdAbs against $A\beta_{(pE3-42)}$ and αSyn will provide a clear rationale to pursue anti-$A\beta_{(pE3-42)}$ and αSyn based immunotherapy and diversify our current portfolio for treating AD.

**Preliminary Data, Experimental Design and Methods:**

**Preliminary Data:** We have recently developed a robust pipeline for the discovery and characterization of high-quality antigen-specific sdAbs. This pipeline has been tested for APOE and CLU proteins and we have successfully identified several anti-APOE and anti-CLU sdAbs, which are currently under evaluation of their efficacy in mouse models of AD. Here, we have immunized a llama with preformed fibrils (PFF) of αSyn and the pyroglutamate form of $A\beta_{(pE3-42)}$ and generated the immune libraries. We have already screened our immune sdAb library and selected dozens of potential binders to Aβ and αSyn after two rounds of biopanning by ELISA assay. We have purified initial sdAbs against $A\beta_{(pE3-42)}$ and αSyn. As our sdAbs cloning strategy includes C-terminal of HA- and 6xHis epitope tags, the sdAbs were expressed in E*. coli* WK6 cells

and purified using Ni-MAC resins. The yields of these sdAbs are in the range of 1-10 mg from 1 L of bacterial culture. We have confirmed their application in ELISA. In addition, the results of immunofluorescence assays showed that our anti-$A\beta_{(pE3-42)}$ clones recognize the fibrillar plaques in brain sections of APP/PS1 mouse as co-stained by X34, but not in WT mouse. The sdAbs were detected using rabbi anti-HA antibody followed by Alexa Fluor 647-conjugated goat anti-rabbit antibody as our sdAbs have the HA epitope tag. Furthermore, the results of immunohistochemistry assays demonstrated that our anti-$A\beta_{(pE3-42)}$ clones recognize the fibrillar plaques in brain sections of APP/PS1 mouse, but not in WT mouse. Therefore, these results highlight that our strategy using preformed fibrils of $A\beta_{(pE3-42)}$ for immunization and panning has led to discovery of sdAbs which can recognize the amyloid plaques.

**Experimental Design and Methods:** For Aim 1, our sdAb library is already generated and screened with clones picked and characterized for $A\beta_{(pE3-42)}$ or $\alpha$Syn binding based on ELISA assays. We will screen the sdAbs by immunoblotting against monomers and pre-fibril forms (PFF) of $A\beta_{(pE3-42)}$ or $\alpha$Syn using native-PAGE. In addition, we will perform ELISA to evaluate sdAbs's selective binding of PFF of $A\beta_{(pE3-42)}$ or $\alpha$Syn. We will utilize the already in-frame HA epitope tag to test for the ability of these sdAbs to work for immunostaining with the brain sections of mouse expressing human amyloid plaques (APP/PS1 mice) and Syn (hy1-αSyn "Line 61" Mouse). Furthermore, we will validate our sdAb immunostaining with human postmortem brain tissues from a well-characterized autopsy cohort of AD and/or DLB cases. For Aim 2, the top 2 lead candidates from the results of immunostaining assays as well as ELISA assays will be selected. The DNA sequence of those sdAbs with or without murine Fc region will be cloned into the AAV vector. For clearing of existing plaques strategy, APP/PS1 mice (n=12/group/sex) will be received a single dose of $1X10^{12}$ vg/mouse of either AAV-anti-$A\beta_{(pE3-42)}$ sdAb, or AAV-anti-$A\beta_{(pE3-42)}$ sdAb-mFc, or AAV-anti-GFP sdAb via tail vein injection at 8 months of age when there are existing plaques in the brains. Behavioral tests will be carried out at 12-moth of age, followed by the sacrifice of mice for histology and biochemistry analysis bulk and single-cell RNAseq analysis. A similar strategy will be used for evaluating the efficacy of anti-SYN sdAb in hy1-αSyn "Line 61" Mice. We will create a bispecific sdAb by linking anti-$A\beta_{(pE3-42)}$ sdAb together with anti-SYN sdAb with a flexible protein linker. The gene cassette will be cloned into the AAV vector. To validate the efficacy of this bispecific sdAbs, we will create an AD mouse model with Lewy-related pathology by crossing APP/PS1 mice with hy1-αSyn "Line 61" Mice. The Aβ pathology and Lewy-related pathology will be characterized in the new line. A similar strategy described above will be used for evaluating the efficacy of the bispecific sdAbs in the new mouse model.

**Proposed One-Year and Long-Term Outcomes:**

For Aim 1, we will continue the discovery and characterization of anti-$A\beta_{(pE3-42)}$ and anti-$\alpha$Syn sdAbs. For Aim 2, We will generate the AAV vector expressing top candidate sdAbs and carry out the efficacy test in mouse models with corresponding pathologies. As breeding cohorts and aging takes a lot of time, we will start breeding a mouse model with AD pathology and Syn pathology, and character the new mouse line. We plan to test the efficacy of bispecific sdAbs targeting both $A\beta_{(pE3-42)}$ and $\alpha$Syn in this new mouse line when the mice have the amyloidosis and Syn pathology.

With the data generated from this funding, we will continue to seek additional external, non-state funding from NIH, industry, foundations to support our efforts to develop novel immunotherapies for AD treatment.

**Year End Progress Summary:**

We have discovered multiple lead candidates of anti-$A\beta_{(pE3-42)}$ and anti-$\alpha$Syn sdAbs. Through various characterization assays, we have selected two lead candidates for anti-Aβ sdAbs clones, 3A11 and 2D10. The results of epitope mapping assay showed that anti-Aβ 3A11 and 2D10 sdAbs recognized distinct epitopes of amyloid-β. The results of immunohistochemistry (IHC) analysis demonstrated that 3A11 and 2D10 can successfully recognize the amyloid plaques in brain sections from APP/PS1 amyloid mouse model. Furthermore, we have demonstrated that those two anti-Aβ sdAbs also recognize amyloid plaques in post-mortem human brain tissues from AD case as evidenced by IHC assay (Figure 1). We sought to evaluate the capability of anti-Aβ sdAbs to cross the blood-brain barrier and effectively bind to amyloid plaques deposited in the mouse brains by performing *in vivo* target engagement studies. Nine-month-old APP/PS1 mice (N=2/group) were treated for four days with daily intraperitoneal injections of either anti-Aβ 2D10 sdAb at 40 mg/kg, or a vehicle control (PBS). Five-hours following the final dose, the mice were euthanized to harvest the brains. The results of immunostaining assays of the brain sections demonstrated that mice injected with 2D10 exhibited robust plaque labeling across the hippocampus and cortical regions. Therefore, we confirmed the ability of sdAbs to cross the blood-brain barrier and bind effectively to amyloid plaques in APP/PS1 amyloid mouse model. We also designed the bivalent sdAbs targeting amyloid plaques by coupling the 3A11 and 2D10 with a flexible protein linker. The bivalent sdAbs demonstrated a superior binding to amyloid plaques than their parental monomeric sdAb, as evidenced by Dot-blotting assays, ELISA assays, and IHC stainings. Currently, we have bred enough APP/PS1 mice for the proposed experiments, they are aging to the point when there are plenty of amyloid pathology. We will carry out the efficacy tests of those sdAbs in these APP/PS1 mice by direct i.p. injections of the sdAbs proteins as well as AAV-mediated delivery method.

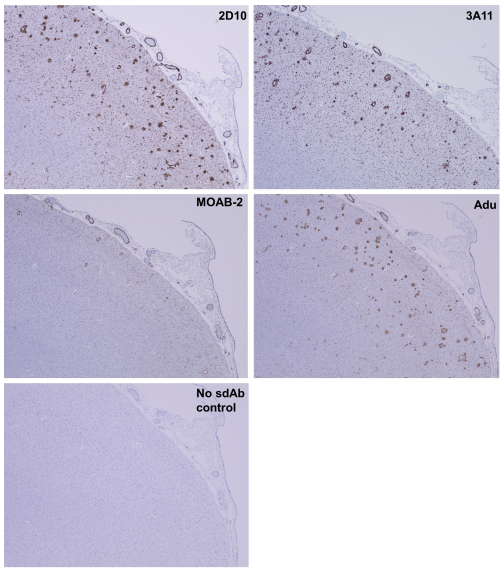



Figure 1. Immunohistochemical analyses of brain sections from a 74-year-old female AD patient staining with 100 ng/ml anti-Aβ sdAb 3A11, or 2D10, pan anti-amyloid antibody 1.2 ug/ml MOAB-2, or 10 ng/ml aducanumab. Magnification is 4x.

For the anti-synuclein sdAbs, we have identified dozens of candidates of anti-Synuclein sdAbs. Results of the affinity ELISA assays demonstrated that the apparent $EC_{50}$ values for these anti-SYN sdAbs are around micro-molar range. Due to the low affinity of these anti-SYN sdAbs, we decided to pursue another round of immunization. We are planning to immunize another llama with the syn fibrils amplified from PD and DLB patients, in hoping of getting high affinity anti-SYN sdAbs from this immune library.

We are currently in prep of a manuscript for anti-amyloid sdAbs. We have filed the invention disclosure with Mayo Clinic Ventures in regarding of anti-amyloid sdAbs. We are planning to submit an R21 grant proposal in this October.

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Retinal Imaging Application in Preclinical Alzheimer's Disease.** Oana Dumitrascu MD, MSc, Richard Caselli, MD, Bryan Woodruff, MD, Yalin Wang, PhD. Mayo Clinic Arizona; Arizona State University; Arizona Alzheimer's Consortium.

**Specific Aims:**

**Specific Aim 1:** To develop a comprehensive database of non-mydriatic retinal images from cognitively unimpaired (CU) amyloid-positive and their age-matched cognitively normal (CN) amyloid-negative controls with the APOE2/2, 2/3, 2/4, 3/3, 3/4, and 4/4 genotypes in the Arizona APOE Cohort, and to characterize pre-clinical AD specific retinal biomarkers in retinal color fundus photographs (CFPs) and optical coherence tomography (OCT).

**Specific Aim 2.** To design and train deep convolutional neural networks (DCNN) models for automatic computation of retinal imaging markers of preclinical AD. Input measures (retinal CFPs and OCT raw images, APOE genotype) derived from two cohorts (CU preclinical AD and matched CN subjects from AZ APOE cohort) will be used to train and test AD screening DCNNs. This development grant will allow us to obtain the comprehensive retinal images needed to **1) study the differential effect of APOE4 allelic dosage on retinal biomarkers of preclinical AD and to 2) train a DCNN model to automatically compute retinal imaging biomarkers for early AD screening and monitoring.**

**Background and Significance:**

The ability to identify individuals in pre-clinical AD stage before its clinical manifestation is a top scientific priority. A CNN using multimodal retinal imaging was tested in symptomatic AD (15). Yet, there are no established highly accurate DL models to detect AD in asymptomatic or minimally symptomatic patients, and to offer them access to disease-modifying therapies or early enrollment in clinical trials. We hypothesize that a deep convolutional neural network (DCNN) could be trained and tested to predict development of AD in cognitively unimpaired (CU).The overarching goal of this study is to build a DCNN that will allow accurate and cost-effective AD prediction and AD monitoring. This will facilitate large-scale monitoring of the risk of developing AD and opportunity for personalized targeted interventions. We aim to train and test DCNN models in preclinical AD stages and fine-tune them for validation and translation into clinical practice for point-of-care AD screening and monitoring. We plan on achieving this by examining the effect of retinal imaging biomarkers (color fundus photographs (CFPs) and optical coherence tomography (OCT)) on AD screening, stratified by APOE4 allelic dosage, and then modulating DCNN models to determine inputs that are highly accurate for AD prediction in CU subjects. We aim to utilize the Arizona APOE and ADRC cohorts of preclinical AD (CU Aβ positive) and their matched cognitively normal (CN) controls Aβ negative, to develop a novel, comprehensive and longitudinal database of non-mydriatic retinal images. We will develop a DCNN model based on comprehensive retinal imaging (CFPs and OCT), APOE genotype and other patient data from preclinical AD subjects. We will first investigate the potential of various retinal imaging biomarkers to specifically identify those that predict AD development, stratified by three levels of AD genetic risk based on APOE4 allelic dosage. Next, we will build DCNN models using retinal imaging and APOE that will accurately discriminate between CU Aβ positive and CN Aβ negative.

**Preliminary Data, Experimental Design and Methods:**

1. Serial CFPs and OCTs will be obtained from pre-clinical AD patients (CU, Aβ positive (CSF or PET)), and 150 matched controls (CN, Aβ negative). The retinal parameters (fractal analysis (CFPs), retinal layers thickness (OCT)) will be compared between the 2 groups. The retinal measures will be stratified by APOE4 gene dosage (two, one, none). Retinal CFPs will be analyzed using previously utilized retinal fractal analysis methodology, that will allow the calculation of retinal vessels (arterioles and venules) tortuosity, inflection, length, branching angle and branching density. Retinal OCT parameters (total retinal thickness, average retinal nerve fiber layer (RNFL) thickness and ganglion cell-internal plexiform layer (GC-IPL) thickness) are automatically calculated by the Topcon software. We will characterize and compare each retinal imaging biomarker measurement as a function of age. For amyloid PET scans, a centiloid cut-off of 20 will be used to determine amyloid positivity, determined to detect moderate to frequent brain amyloid burden as from pathological assessment.

2. A DCNN will be developed based on binary vessel segmentation of retinal CFPs. We will evaluate the U-net encoder classifier, and the gradient-weight Class Activation Mapping to confirm our previous research that retinal vascular tortuosity and inflection correlate with neurocognitive dysfunction and may predict AD. Furthermore, to develop an APOE-stratified comprehensive retinal imaging framework for pre-clinical AD prediction, we will use the age, gender, ethnicity, APOE4 allelic dosage and retinal OCTs as complementary data to the previous retinal automated diagnostic model. We will have a joint model to increase the confidence of the network. The model accuracy to discriminate between CU Aβ positive and CN Aβ negative individuals will be calculated using AUC and dynamic discrimination index.

**Proposed One-Year and Long-Term Outcomes:**

1) to characterize retinal changes in presymptomatic AD and their correlation with APOE4 allelic dosage, neurocognitive and brain volumetric measures.
2) to train and test DCCN models for automated computation of retinal imaging biomarkers for pre-symptomatic AD.

**Year End Progress Summary:**

**Aim 1:** We obtained non-mydriatic retinal CFPs and OCT images from 162 cognitively intact subjects (APOE 2.0 cohort), 36 amyloid-positive, 89 amyloid-negative, and 37 pending amyloid status. APOE4 allelic dosage: 73 zero, 57 one, 20 two alleles, 12 pending. Retinal imaging collection is on track; lagging is amyloid status determination in 37 subjects, pending either amyloid-PET imaging or results quantification. Only retinal images that had appropriate quality for retinal fractal and OCT analyses were included in subsequent analyses.

**Retinal fractal analysis** was done in 92 subjects, 41 APOE4 carriers (16 homozygous and 25 heterozygous) and 51 APOE4 non-carriers. More APOE4 carriers were amyloid positive compared to non-carriers (61% vs 15%, P <0.0001). Homozygous carriers were significantly younger (mean (SD) age of 63.5 (6.9) years), compared to heterozygous carriers 72.5(7.3) and non-carriers 70.59 (7.9). There were significantly less Hispanic or Latino among the APOE4 carriers compared with non-carriers (2.6% vs 20.8%, p=0.02). Using GEE linear regression adjusted for age, sex, and ethnicity, APOE4 carriers had significantly lower arterial branching angle compared to non-carriers (B= -4.9, 95%CI [-9.21 – -0.719], p= 0.02). APOE4 homozygotes had a significantly lower arterial branching angle (B= -8.43, 95%CI [-15.9 – -0.883], p= 0.029), whereas heterozygotes did not show statistically significant differences (p=0.138)). We compared retinal vascular fractal measures among 39 amyloid positive and 55 amyloid negative subjects.

Preclinical AD cohort was significantly older than the control cohort and included non-significantly more male and less Hispanics. GEE analysis after adjusting for age, gender, ethnicity demonstrated that preclinical AD patients had a significantly lower retinal venous branching angle as compared to controls (B= -7.701, 95% CI [-12.219 – -3.184], p<0.001), while the lower retinal arterial branching angle in preclinical AD approached near significance (B= -5.742, 95% CI [-12.221 – 0.737], p= 0.082).

Pending analyses will investigate the potential causal mediation role of the APOE allelic dosage in the relationship between amyloid-PET, retinal vascular measures and cognitive performance.

**OCT preliminary analysis** was done in 71 subjects, 27 preclinical AD (34% men, median age of 75 years (IQR: 64-81)) and 44 controls (23% men, median age 70 years (IQR: 64-77)). Mean (SD) overall RNFL thickness of the right eye was significantly lower in the preclinical AD compared to controls (90.05 (19.81) vs 98.58 (12.64), p = 0.034). That difference was most prominent in the inferior quadrant (median [IQR] 101[83-124] vs 116[106-128], p = 0.004). No statistically significant differences were found in the GCIPL thickness between the 2 groups. All OCT parameters significantly correlated between right and left eyes.

Challenges encountered: retinal images imperfections when retinal imaging is obtained without dilation. We worked on developing an automated algorithm to remove the artifacts from retinal color photographs while preserving their structural consistency (PMCID: 10513403, PMCID: 10329768).

42 (29.5%) subjects underwent both retinal imaging and brain MRI, and 114 (80.2%) underwent retinal imaging and cognitive analysis. Future analyses will include correlations between retinal, neuroimaging and cognitive measures, using age and APOE as co-variates.

**Aim 2:** Our prior CNN model based on U-net and binary vessel segmentation reached an accuracy of 72.7% on the testing dataset to distinguish preclinical AD (19 subjects, 65 images) vs controls (29 subjects, 102 images), despite greater than 90% accuracy to classify AD from controls. Hence in the past 6 months, we developed and validate **PreADFound**, a novel BERT (bidirectional encoder representations from transformers)-style self-supervised learning CNN, pretrained on 178,803 unlabeled macula-centered CFPs from 87,245 UK Biobank participants with AD and non-AD. In our Mayo APOE testing dataset of CFPs from cognitively normal subjects (amyloid-positive (96 images, 32 subjects) and amyloid-negative (166 images, 56 subjects)), the PreADFound model achieved AUROC of 0.8628, 85.11% accuracy, and kappa score of 0.655 for preclinical AD classification. The attention heatmaps derived from preclinical AD CFPs pointed out retinal regions in the supero-temporal or infero-temporal vascular arcades, in the optic nerve proximity. We are currently training a multi-modality model on preclinical AD images, adding age, sex and APOE status.

Patent application 04/20204: D24-186 A BERT-Style Self-Supervised Learning CNN for Disease Identification from Retinal Images. NIA R01 re-submission including this new self-supervised CNN model is anticipated for August 2024 (Co-PIs Oana Dumitrascu (Mayo Clinic) and Yalin Wang (ASU School of Computing and Augmented Intelligence)).

**Below are key abstracts, publications and oral presentations form our work:**
1. APOE status impacts retinal arteriolar fractal dimension in individuals with normal cognition. American Neurological Association Annual Meeting, September 2024, Orlando, FL.

2. Retinal vascular fractal analysis in cognitively intact individuals at risk for Alzheimer's Disease. Association of Research in Vision and Ophthalmology Annual meeting, May 2024, Seattle, WA.

3. Retinal Nerve Fiber Layer Thinning in Pre-Symptomatic Alzheimer’s Disease: A Case-Control Study. North American Neuro-ophthalmology Society annual meeting, Honolulu, HI, March 2024.

4. Self-supervised neural network trained on retinal photographs can identify pre-symptomatic Alzheimer’s disease. American Neurological Association Annual Meeting, September 2024, Orlando, FL.

5. Cognitively intact apoe4 carriers have narrower retinal arterial branching angles than non-carriers. Mayo Clinic Arizona Academic Excellence Day, May 2024, Phoenix, AZ.

6. Optical coherence tomography could discriminate cognitively intact individuals at risk for Alzheimer’s disease. Mayo Clinic Arizona Academic Excellence Day, May 2024, Phoenix, AZ.

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**APOE4 Modulation of Brain and Retinal Imaging Vascular Biomarkers in Pre-clinical Alzheimer's Disease.** Oana Dumitrascu, MD, MSc, Leslie Baxter, PhD, Richard J. Caselli, MD, Bryan Woodruff, MD, Yuxiang Zhou, PhD, Simona Nikolova, PhD, Gina Dumkrieger, PhD. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

**Specific Aims:**

**Specific Aim 1.** To characterize the quantitative brain MRI vascular measures and retinal vascular features in a cohort of subjects with intact cognition, with and without amyloid positivity, stratified by APOE ε4 carrier status.

**Specific Aim 2.** To test the hypothesis that brain and retinal vascular changes contribute to neurocognitive function, under the modulation of APOE4 allelic dosage. We will comparatively relate brain MRI and retinal vascular measures of cerebrovascular disease to the measures of neurocognitive function.

**Background and Significance:**

The vascular hypothesis of AD assumes that brain microcirculation disruption not only contributes to amyloidopathy but also initiates a non-amyloidogenic pathway of vascular-mediated neuronal dysfunction and injury, with increased permeability of blood vessels, leakage of blood-borne components into the brain, and, consequently, neurotoxicity. The toxic effects of Aβ and apolipoprotein E (ApoE) are likely to induce a non-cerebral-amyloid-angiopathy-related degeneration of endothelial cells, independently of cerebrovascular disease; however, some of the observed structural changes may just arise with age. Brain vascular dysfunction in AD has been studied to evaluate the AD pathophysiology and identify specific therapeutic targets (12-14). BBB dysfunction on magnetic resonance imaging takes place early in the disease course in AD-specific brain regions. White matter hyperintensities mediate the association between blood-brain barrier leakage and information processing speed. White matter pathology is suggested to form a link between leakage and decline of information processing speed in older individuals with and without cognitive impairment (21). Region-of-interest-based cerebral blood flow measurements differentiated MCI from healthy controls (22). Studies have shown that APOE4 induces cerebrovascular dysfunction directly and indirectly (26).

As BBB and blood-retina barrier (BRB) have similar pathophysiology (27), multiple static and dynamic retinal vascular biomarkers were also investigated across the AD spectrum (28-33). The retinal vascular pathology in AD was characterized using various retinal imaging technologies., Retinal vascular tortuosity was proposed to improve the detection of the cerebral amyloid status as determined by 8F-florbetaben PET (46). Retinal arteriolar central reflex to vessel width ratio measured in digital retinal photographs was noted to be significantly higher in APOE ε4 allele carriers as compared with noncarriers in the Australian Imaging, Biomarkers, and Lifestyle study of aging (42). Therefore, the retina may allow for noninvasive monitoring of the effects of APOE ε4 on the cerebrovascular disease. We hypothesize that the vascular changes in the brain and retina vary between APOE ε4 carriers and non-carriers in pre-clinical AD and normal controls, and that the relationship between vascular changes on brain MRI and retinal color photographs and cognitive performance would differ based on APOE genotype.

**Preliminary Data, Experimental Design and Methods:**

We will include all participants from AZ APOE cohort that underwent brain MRI with the following sequences: 3D AX T1 MPRAGE 1MM, 3D T2 SPC FLAIR, WIP_3D_pCASL_5delay_3.5iso, AX T2 TSE Q9R910011, AX DTI 2X2X2, gre_field_mapping, WIP_AX T2STR SWI, FMRI REST STATE. Some participants will undergo non-mydriatic retinal with retinal color fundus photography and OCT using MAESTRO-2 (Tocpon Inc.).

In this exploratry analysis, we will:

1) compare cerebral perfusion status, brain gray matter and white matter volumes, white matter hyperintensity and microbleeds volume and counts, and the presence of other cerebrovascular pathology on brain MRI between APOE4 carriers and non-carriers, controlling for age, and the presence of tradiotional vascular risk factors.
2) compare retinal microvascular parameters between APOE4 carriers and non-carriers, controlling for age, and the presence of tradiotional vascular risk factors.
3) compare retinal and brain microvascular parameters between pre-clinical AD and age-matched controls.

**Proposed One-Year and Long-Term Outcomes:**

We plan to complete the proposed aim 1 within the 1-year timeframe, by analyzing data from all included subjects in the Arizona APOE cohort. Prospective follow-up with repeated amyloid PET, retinal imaging and cognitive assessments every 2 years, will allow to determine the association between vascular disease progression and amyloid burden and cognitive performance. As BBB dysfunction on MRI in AD-specific brain regions and BRB dysfunction on color fundus photographs takes place early in the disease course, reducing cardiovascular risk factors may represent a promising intervention for AD prevention, especially in APOE4 carriers.

**Year End Progress Summary:**

**T2/FLAIR and GRE analysis**: we included 66 APOE4 heterozygotes, 19 APOE4 homozygotes, and 109 APOE4 non-carriers, majority female (74.2%) and Caucasian (80.9%), mean(SD) age 66.1(10.7), mean (SD) education (years) 16.4(2.4). The 3 groups were matched for sex, age, race, education ($p>0.05$ for all). Most subjects (62.3%) had mild T2 WMHI burden (67.1% APOE4 carriers, 58.7% non-carriers), Fazekas grade 1 being the most common finding (38.7% periventricular, 49.0% subcortical). 92.3% had no CMBs (89.4% APOE4 carriers, 94.5% non-carriers). Only 11 (6.7%) had cerebral infarcts. There was no statistically significant difference in T2 WMHI burden ($p=0.26$), periventricular ($p=0.63$), subcortical Fazekas grade ($p=0.50$), and CMB count ($p=0.28$) between the APOE4 homozygotes, heterozygotes and non-carriers. However after correction for age, gender, ethnicity and vascular risk factors, APOE4 carriers had greater GRE burden compared to non-carriers.

Amyloid positive (24) and negative (48) groups were not different based on cigarettes smoking, diabetes, gender, Hchol, HTN, obesity, race, but amyloid positive were significantly older (71.2 vs 63.2, P= 0.000). T2 WMHI or GRE burden were not different between amyloid positives and negatives, after correction for age, gender, ethnicity and vascular risk factors. Pending topographic analysis for lesions' localization.

Given the difficulty of detecting these subtle alterations through unaided human eye, we proposed

a novel approach called Relative Scoring Network (RSNet), that integrates relative learning and contrastive learning to detect preclinical AD patients based solely on their MRI scans. In addition, RSNet can generate a score that can be used to aid clinicians in gauging the severity of preclinical

AD. We demonstrated the feasibility of the idea and its potential, especially the differentiation between healthy individuals and those in the preclinical stage of AD, utilizing the OASIS-3 dataset. We will next test this model in the Mayo APOE 2.0 MRI dataset.

**Whole-brain voxel-based Quantitative Susceptibility Mapping analysis:** The participants' mean (SD) age was 69(8), 75.4% were female and 35% were APOE ε4 carriers. Higher iron accumulation in the right hippocampus, right amygdala, right orbitofrontal and left frontal infero-orbital zones was associated with lower AVLT-LTM scores, after controlling for age, sex, and education. The APOE ε4 carriers had increased iron in the right parahippocampal region, bilateral gyrus rectus and in the right putamen. There were significant differences in functional connectivity between these regions and APOE ε4 groups in the right hippocampus to the ipsilateral temporal lobe and amygdala; the bilateral gyrus rectus to the temporal and frontal lobe, and the right putamen to the left supplemental motor area and right orbito-frontal cortex.

**Pseudo-continuous (pC) Arterial Spin Labeling analysis**: In the entire cohort, arterial transit time (ATT) and cerebral blood flow (CBF) were significantly lower in left-sided anterior choroidal artery (AchA) territories ($p<0.001$, $p=0.004$) and CBF was lower in left-sided posterior cerebral artery (PCA) territories ($p<0.001$), compared to the right-side territories. When stratified by amyloid status, ATT remained lower in left-hemispheric AChA territories in amyloid-positive patients only ($p=0.017$). Similarly, when stratified by APOE4 status, ATT remained lower in left hemispheric AChA territories in carriers ($p=0.001$) only. In PCA territory, left-sided CBF remained lower in all stratifications ($p<0.05$), without significant hemispheric differences in ATT.

CBF whole-brain analysis: CBF maps were co-registered to anatomical T1-weighted MP rage using the reference image and then normalized to MNI coordinates to obtain average region of interest perfusion from an automated anatomical grey matter atlas (AAL V3.7)). Greater CBF in APOE4 carriers c/w non-carriers and amyloid positive c/w negative in certain brain locations (bilateral frontal, temporal, caudate, putamen, thalamus, basal ganglia). In APOE4 carriers above age 60, bilateral thalamus CBF was increased after adjustment for age, sex, education years.

**Retinal vascular analysis:** Using GEE linear regression adjusted for age, sex, and ethnicity, APOE4 carriers had significantly lower arterial branching angle compared to non-carriers (B= -4.9, 95%CI [-9.21 – -0.719], p= 0.02). APOE4 homozygotes had a significantly lower arterial branching angle (B= -8.43, 95%CI [-15.9 – -0.883], p= 0.029), whereas heterozygotes did not show statistically significant differences (p=0.138)). Preclinical AD cohort was significantly older than the control cohort and included non-significantly more male and less Hispanics. GEE analysis after adjusting for age, gender, ethnicity demonstrated that preclinical AD patients had a significantly lower retinal venous branching angle as compared to controls (B= -7.701, 95% CI [-12.219 – -3.184], p<0.001), while the lower retinal arterial branching angle in preclinical AD approached near significance (B= -5.742, 95% CI [-12.221 – 0.737], p= 0.082).

**Pending:** causal mediation role of the APOE genotype and age in the amyloid-vascular biomarkers -cognition correlation. Interaction between retinal and brain vascular biomarkers in subjects with normal cognition, stratified by the amyloid status. Optimization of a deep learning model to identify vascular biomarkers of preclinical AD on brain and retinal imaging unidentifiable by the human eye.

**Below are key abstracts and publications and oral presentations form our work:**

1. Samantha Brown, Richard Caselli, Bryan Woodruff, Oana Dumitrascu. APOE Genotype, White Matter Hyperintensities, and Cerebral Microbleeds in a Cohort with Intact Cognition. Poster presented at the American Academy of Neurology Annual Meeting, Denver, CO, April 2024.

2. Samantha Brown, Gina Dumkrieger, Bryan Woodruff, Lunt Curtis Richard Caselli, Yuxiang Zhou, Oana Dumitrascu. Interhemispheric Hippocampal Perfusion Asymmetry in Individuals with Intact Cognition. American Neurological Association Annual Meeting, Orlando, FL, September 2024.

3. Oana Dumitrascu, Leslie Baxter, Bryan Woodruff, Jennifer Nikolova, Curt Luntis, Richard Caselli, Yuxiang Zhou, Simona Nikolova. Increased cerebral iron burden leads to altered functional connectivity and decreased memory. American Neurological Association Annual Meeting, Orlando, FL, September 2024.

4. Thakur Nupur, Paul Riti, Baoxin Li, Dumitrascu OM, Yuxiang Zhou. Harnessing Deep Relative Learning for Prediction of Preclinical Alzheimer's Disease using MRI. International Conference on AI in Healthcare, 2024.

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Interventions for Those Caring for Those with Cognitive Impairment (CarePRO-VA).** Dona E.C. Locke, PhD, David Coon, PhD, Andrea Cuc, LCSW, Jeanne Eilertsen, BA, Deborah L. Brostrum, BS. Mayo Clinic Arizona; Arizona State University; Arizona Alzheimer's Consortium.

**Specific Aims:**

The specific aim for the 2023-2024 year was for the Mayo Clinic research team to run two additional CarePRO-VA research sessions in order to contribute additional efficacy data as well as ongoing dissemination and implementation of the program in the Mayo Clinic practice.

We also planned to support analysis of data from our previous sessions and ASU in the 2023-2024 period. We already have IRB approval to share deidentified data with ASU.

**Background and Significance:**

In the recent Alzheimer's Association facts and figures report, Arizona shows the highest average amount of caregiving hours out of all states in the nation. Our goal is to continue to build support programs that help our caregivers in their caregiving journey. Mayo Clinic already has a clinically available multi-component therapy for those with MCI and their partners, the HABIT Healthy Action to Benefit Independence & Thinking ® program. Though partners are included, the program itself is very patient oriented. CarePRO VA has the potential to support caregivers very directly and with dissemination of a validated, Zoom-based, option, widen access to the program across Arizona.

**Preliminary Data, Experimental Design and Methods:**

During the 2021-2022 year, we succeeded in training the Mayo Clinic staff on CarePRO and ran two sessions in combination with ASU (n=17), contributing data that showed that the program could be successfully implemented at a second site.

During the 2022-2023 year, the Mayo Clinic team ran two sessions of the research CarePRO intervention contributing additional efficacy research data for the virtual adaptation of the CarePRO intervention for caregivers. That involved an additional 15 caregiver participants recruited from the Mayo Clinic Practice.

With the 2023-2024 funding year, we increased our planned recruitment to CarePRO virtual from an original group of 20 families from the Mayo Clinic Arizona practice up to 50 caregivers.

**Year End Progress Summary:**

As of July 2024, we completed an additional two sessions adding 14 additional caregiver participants (total N so far from Mayo Clinic = 46). Assessments were again conducted at baseline (pre-intervention or T1), immediately post intervention, and follow-up (approximately 12 weeks after baseline or T3). We have shared that deidentified information with the ASU team (with IRB approval) for entry into the master dataset for CarePRO VA. We continue to communicate with ASU and remain available to help support data analysis, presentations, or manuscript writing with that dataset.

Dr. Coon presented preliminary data at the Spring AAC public conference.

**Proposed One-Year and Long-Term Outcomes:**

By July 2025, it is the goal of the Mayo Clinic team to have run two additional sessions to demonstrate ongoing success in recruitment and delivery of the program as well as consistency of the quality of the data collected at Mayo Clinic when compared to ASU. We remain available to support data analysis and manuscript production. Dr. Locke has suggested to Dr. Coon possible abstract submission for the AAC academic conference for the fall of 2024.

We continue to aim to offer the CarePRO program routinely to our clinical practice.

# ARIZONA ALZHEIMER'S CONSORTIUM
# 2023-2024 Scientific 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. Failed anti-amyloid therapies have been blamed on being started too late, resulting in new disease modifying 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 3300 participants from which were selected our study population for further testing. We have completed one or more epochs of neuropsychological testing on 1068 individuals including 594 APOE e4 noncarriers, 346 e4 heterozygotes, and 126 e4 homozygotes with followup durations of up to 29 years (average is approximately 10.9 years) providing data for longitudinal studies. We have nearly 3000 plasma

and serum samples on roughly 375 individuals, and DNA on all. 497 have immortalized cell lines established including all with brain imaging. We have completed whole genome sequencing in 537 participants and have ongoing MRI enrollment with 167 completed to date. 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).

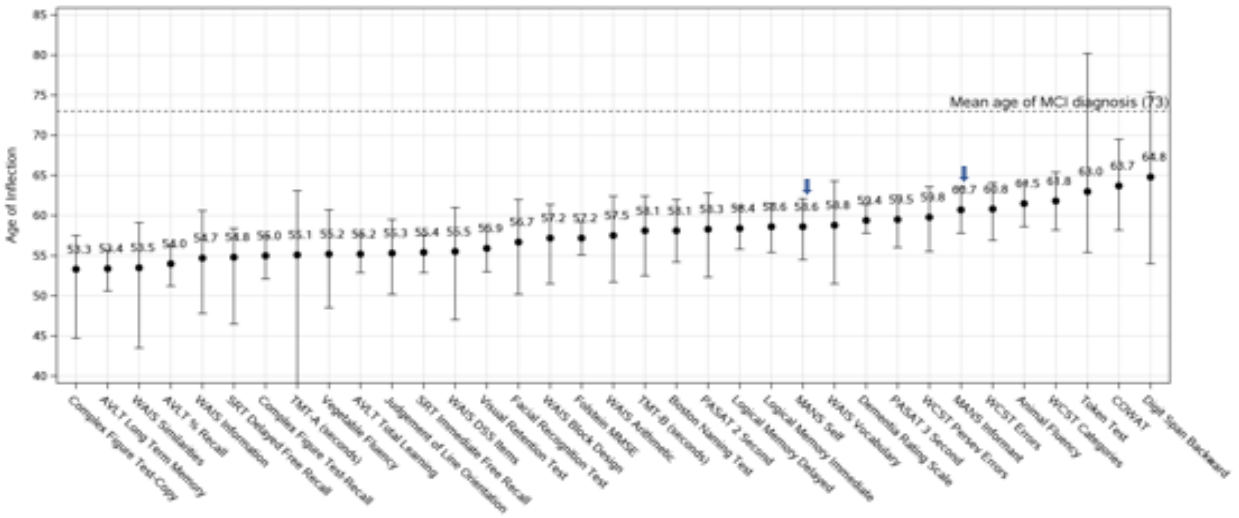
**Proposed One-Year and Long-Term Outcomes**:

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. Support an initial study examining the correlation of genomic diversity with cognitive aging trajectories and clinical outcomes
5. Use supporting funds to include MRI studies of cohort members that will:
    a. Establish an ongoing resource for future research efforts
    b. Support an 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

**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, David Brafman, Michael Sierks, Molly Maxfield, Li Liu), USC (Berislav Zlokovic), Mayo Clinic (Oana Dumitrascu, Otto Pedraza, Leslie Baxter, Cynthia Stonnington), and Banner Alzheimer Institute (Eric Reiman and his team).
4. We observed an APOE ε4 allele dose effect on plasma neurofilament light chain levels in our cohort, which correlates with smaller hippocampal volumes, regional tau deposition, and memory performance (9).
5. Utilizing a machine learning algorithm applied to longitudinal neuropsychology measures in our cohort, we were able to predict conversion to mild cognitive impairment 1-2 years prior to clinical diagnosis with 97% accuracy (10).
6. A manuscript describing use of this project's data for retinal analyses in Alzheimer's disease has been accepted for publication (11).

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# MIDWESTERN UNIVERSITY

# PROJECT PROGRESS REPORTS

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Involvement of the Brain-Muscle Axis in Western Diet Induced Alzheimer's Pathology.** Layla Al-Nakkash, PhD, Thomas Broderick, PhD, Minsub Shim, PhD, Ramesh B. Jeganathan, PhD, James Porter, PhD, Maria Colon. College of Graduate Studies, Midwestern University; Auburn University; Ponce Health Sciences University, Puerto Rico; Arizona Alzheimer's Consortium.

**Specific Aims:**

1. Determine ability of exercise to prevent high-fructose high-sucrose (HFHS)-induced build-up of Alzheimer's-associated brain markers.
2. Determine ability of exercise to prevent HFHS-induced Alzheimer's-associated cognitive decline.
3. Determine ability of exercise to prevent HFHS-induced metabolic syndrome and the diabetic-obese phenotype.
4. Determine the ability of exercise to promote skeletal muscle changes in muscle type and myokine release.

**Background and Significance:**

Obesity resulting from ingestion of high energy foods such as high-fat diet (HFD), 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. Given the epidemic of obesity in the US, this proposed study is relevant. Although the adverse effects of obesity are well-known, its underlying mechanisms remain to be determined. It has been recently shown that HFHS induces senescence in mice. Given the strong association between senescence and aging, this finding suggests that senescence may contribute to obesity-associated neurocognitive decline.

Exercise is commonly recommended by physicians to assist in reversing obesity. Exercise has been shown to improve hippocampal-dependent learning and memory in older individuals and voluntary wheel running has been shown to ameliorate some of the memory dysfunction in HFD C57BL/6J mice. Our group has recently demonstrated that exercise training (along with resveratrol) provided benefits in cardiac function and aortic elastin morphology in the 3xTg mouse model of AD.

**Preliminary Data, Experimental Design and Methods:**

We utilized male *C57BL/6J* mice purchased from Jackson labs (aged 4-weeks), acclimated for 1-week, and then randomly assigned to one of 4 groups: lean controls-sedentary (fed normal standard chow and water), or lean with exercise, a group fed high fat diet containing: 60% fat, 20% protein and 20% carbohydrate from Dyets Inc) along with 42g/L liquid sugar (sucrose and fructose combined), i.e. HFHS and a group fed HFHS and exercised. The exercise regimen was set at 30 min/day for 5 days/week, for the study duration of 12 weeks. Exercise intensity was 12 meters/min (i.e. the American Heart guidelines for 30 minutes of moderate activity, for a total of 150 minutes/week). Mice were euthanized at the completion of the 12-week study and tissues harvested and maintained at -80$^{o}$C until use.

**Proposed One-Year and Long-Term Outcomes:**

We hypothesized that administration of exercise would improve outcomes in the HFHS-fed diabetic-obese mice. We predicted that regular moderate intensity exercise would prevent the detrimental effects of diet-induced obesity on cognitive dysfunction and AD–like pathology and improve skeletal muscle changes.

**Year End Progress Summary:**

**Aim 1. Determine ability of exercise to prevent HFHS-induced build-up of Alzheimer's-associated brain markers.**

We examined the effect of HFHS diet in male mice and assessed the influence of exercise on the associated changes in brain markers for Alzheimer's Disease. Data to date indicates that HFHS induces increased the level of protein expression of pGSK-3B, and increases the pGSK-3B/GSK-3B ratio, and exercise reduces this to levels seen in lean controls. We determined that HFHS diet increases CP13, ADAM 10 and Caspase-3 levels and exercise reduces levels to those seen in leans. Further markers are being processed.

**Aim 2. Determine ability of exercise to prevent HFHS-induced Alzheimer's-associated cognitive decline.**

Due to conflicts in scheduling the use of the behavioral testing equipment we were unable to complete this aim with the last cohort of mice. We plan to repeat this study in Summer 2024 and have secured use of all required behavioral testing equipment and foresee no issues with completion of open field testing and novel object recognition testing. Analyses will be using ANY-MAZE software.

**Aim 3. Determine ability of exercise to prevent HFHS-induced metabolic syndrome and the diabetic-obese phenotype.**

We monitored murine weight throughout the diet and exercise study and note that HFHS fed mice gained significant weight over the diet period, but exercise significantly reduced the amount of weight gain. This was associated with comparable changes in adiposity. We have data suggesting that HFHS mice, are diabetic (evidenced by increased serum glucose and insulin levels), and exercise prevented such changes. We are currently assessing serum leptin/GLP levels.

**Aim 4. Determine the ability of exercise to promote skeletal muscle changes in muscle type and myokine release.**

We examined the effect of HFHS and/or exercise on skeletal muscle and compared it to lean controls. in male mice. Skeletal muscle comprises of bundles of muscle fibers and oxidative muscle fibers have a higher mitochondrial content. Consumption of a HFHS diet induces changes in skeletal muscle fiber type towards a glycolytic type. After 12 weeks of the HFHS diet we found that exercise enhanced mitochondrial biogenesis independently from the AMPK/PGC-1α pathway. Furthermore, we found that DRP-1 which interacts with other mitochondrial outer membrane receptors, played a role in stimulating mitochondrial biogenesis and mitophagy. Overall, our findings imply a beneficial impact of moderate-intensity exercise in preserving oxidative capacity in the muscle of obese mouse model.

Future grant applications, publications and collaborations that arose from the research:

Publications: one publication was published in June 2024 in Nutrients, "Moderate-intensity exercise enhances mitochondrial biogenesis markers in the skeletal muscle of a mouse model affected by diet-induced obesity." Jun, Knight, Broderick, Al-Nakkash, Tobin, Geetha and Babu. This arose from a collaboration with Dr. Ramesh Babu at Auburn University. The PI's (Al-Nakkash, Shim, Lee and Broderick) on the project have a second manuscript in preparation aiming to address the role of exercise brain markers for AD which is likely ready for submission August 2024.

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Assessing the DNA Binding Properties of the Human Telomere Protection Protein RAP1.**

Nancy Bae, PhD, Mark J. Swanson, PhD. College of Graduate Studies, Midwestern University; Arizona Alzheimer's Consortium.

**Specific Aims:**

**Specific Aim 1. Determine RAP1 binding using EMSA**.

**Specific Aim 2. RAP1 binding sites library construction and screening**.

RAP1 (TERF2IP) is a telomeric protein that is responsible for maintaining genome stability by preventing non-homologous end-joining of chromosome ends. RAP1 has a conserved myb domain, which in other proteins is responsible for binding to DNA. However, human RAP1 does not bind to telomeres, and it is recruited to telomeres by another member of shelterin that has its own myb domain. Because of this conserved feature, we tested RAP1 for DNA binding and found it bound to telomere-like sequences in a bacterial one-hybrid system. Through a yeast 2-hybrid screen, we found that RAP1 interacts with TET3, a dioxygenase that converts 5-methylcytosine (5mC) to 5-hydroxyl-methylcytosine (5hmC) by oxidation, which is the first step in a demethylation cascade. TET3 is recruited to gene promoters and activates silenced genes. Our discoveries of RAP1's binding to telomeric sequences and the interaction of RAP1 with the transcription factor TET3 led us to hypothesize that RAP1 binds to a set of promoters, recruits transcription factors such as TET3, and alters the methylation state of the target genes to regulate their expression. There were two aims to this project: (1) Determine RAP1 binding using EMSA, and (2) identify RAP1 binding sites through a library screen. The *working hypothesis* for the first aim is that both cell extracts and recombinant RAP1 proteins will show binding of RAP1 to telomere-like sequences. The *working hypothesis* for the second aim is that we will be able to identify additional RAP1 consensus binding sites within the human genome.

**Background and Significance:**

The ends of human chromosomes are protected from illegitimate fusion and nucleolytic degradation by a six-membered protein complex called shelterin. Of the six subunits, three of the subunits bind to telomeric sequences, while the other three are recruited to telomeres by the DNA-binding subunits. RAP1 is recruited to telomeres through the TRF2 subunit, and once recruited, RAP1 protects ends from non-homologous end-joining. RAP1 was first identified in *Saccharomyces cerevisiae* as a transcription factor, regulating gene expression by binding promoter DNA through its myb domain. Although human RAP1 has a myb domain, RAP1 is recruited to telomeres through TRF2 that binds to telomeric DNA sequences through its own myb domain. For more than a decade, whether human RAP1 can bind to DNA has been approached since its direct binding would solidify a role in transcription regulation.

Through performed chromatin immunoprecipitation (ChIP) coupled with ultrahigh-throughput sequencing using RAP1 knockout mice and human cell extracts, two groups speculated numerous potential RAP1 binding sites throughout the genome. Notably, neither groups' data overlapped, nor did they show physical binding of RAP1 to DNA. To this end, our lab tested whether human RAP1 can bind to telomere-like sequences using a bacterial one-hybrid system. RAP1 bound to DNA through its myb domain with a similar strength as TRF2 binding to DNA.

TET3 is a dioxygenase enzyme responsible for the demethylation that converts 5-methylcytosine (5mC) to 5-hydroxyl-methylcytosine (5hmC), which is the first step in a demethylation cascade. In mammalian cells, methylated DNA is transcriptionally inactive while demethylated DNA is transcriptionally active. Hence, TET3 is suggested to be involved in gene activation. Studies have shown that TET3 regulates the 5mC levels and also affect telomere loss and chromosome fusions when it is knocked out in mouse embryonic stem cells, suggesting TET proteins play a significant role in regulating methylation levels at telomeres. Neuronal TET3 does not bind to DNA. Coincidentally, in an effort to understand the extratelomeric functions of RAP1, we performed a yeast 2-hybrid screen and identified TET3 as an interacting protein of RAP1. Given our data showing RAP1 binds to DNA, and RAP1 interacts with TET3, we hypothesize that RAP1 can bind to non-telomeric sites in the genome, recruit a transcription cofactor, and modulate gene expression in neuronal cells.

**Preliminary Data, Experimental Design and Methods:**

The B1H system can identify DNA sequence specificity of DNA binding proteins. It consists of 2 plasmids and a bacterial reporter strain. Plasmid 1 expresses a protein of interest (RAP1) as a fusion to a subunit of *E. coli* RNA polymerase. Plasmid 2 has DNA binding sites (telomere-like sequences) near the promoter of a polycistronic reporter encoding two selective marker genes.

If the fusion product on Plasmid 1 binds to the binding site on Plasmid 2, *i.e.,* if RAP1 binds to the telomere-like sequences, the cells will express both selective marker genes and will be able to grow in the presence of competitive inhibitor. Our experiments showed that RAP1 binds to telomeric sequences. We also showed that RAP1 can bind to DNA independent of its recruiting partner in shelterin, TRF2, and RAP1 binds these telomere-like sequences with a similar strength as full length TRF2. Although RAP1 can bind telomere-like sequences, these sequences may not represent the strongest binding consensus, or RAP1 may have multiple sequence binding motifs.

**Proposed One-Year and Long-Term Outcomes:**

**Specific Aim 1. Determine RAP1 binding using EMSA**.

Aim 1a. The B1H experiment shows that full length human RAP1 and the myb domain of RAP1 can bind to human telomeric sequences. To verify the B1H results, we want to test RAP1 from human cells for DNA binding. For this, we will use an electrophoretic mobility shift assay, or EMSA. EMSA is used to determine the sequence-specific binding properties of a protein. We will incubate oligonucleotides consisting of telomeric DNA sequences with both whole cell extracts and nuclear extracts from human U251 and SH-SY5Y cell lines. U251 and SH-SY5Y cells are glioblastoma and neuroblastoma cells lines, respectively. When resolved on an agarose gel, the oligonucleotides alone will migrate rapidly, but when they are bound by a protein, there will be a shift to a slower mobility. A commercially available chemiluminescent detection-based kit will be utilized to analyze the binding capability of RAP1. To show that RAP1 is causing the shift in the EMSA, an antibody to RAP1 will be included in the sample. When the RAP1 antibody binds to the RAP1 protein/DNA complex, the band will be shifted to a slower mobility than the DNA-protein complex (a supershift). This will validate the B1H result that RAP1 is binding to DNA directly.

Aim 1b. We will incubate oligonucleotides consisting of telomeric DNA sequences with purified, recombinant RAP1 expressed in *E. coli*. When resolved on an agarose gel, the oligonucleotides alone will migrate rapidly, but when they are bound by RAP1, there will be a shift to a slower mobility. An EMSA supershift experiment will be carried out using RAP1 antibody for this portion of the experiment as well. This will show that RAP1 itself binds DNA without being recruited by other DNA binding proteins.

**Specific Aim 2. RAP1 binding sites library construction and screening**.
Yang *et al.* (2011) suggested that human RAP1 indirectly associates with interstitial sequences in the genome. Our preliminary binding data show that RAP1 can bind telomere-like sequences directly. Interestingly, in a study of 104 transcription factors in mice, Badis *et al*. (2009) found that about half of the proteins recognized multiple distinct sequence motifs. Thus, we want to find additional binding sites of RAP1 within the human genome. Binding sites of greatest interest would be located in the promoter region of a gene, indicating that the gene is most likely regulated by RAP1. Identifying genes where RAP1 binds near the promoter will solidify the notion that human RAP1 works as a transcription factor. Jolma *et al.* (2013) analyzed over 830 binding sites of sequence-specific binding human transcription factors. They concluded that when they compared binding by full-length transcription factors or only their DNA binding domains, both bound to similar DNA sites. Thus, only the RAP1 myb domain can be used in the library screen, and we expect to find DNA binding sites that the full-length protein would bind *in vivo*.

To identify RAP1 binding to non-telomeric motifs, we will use the B1H system. Based on the Meng *et al.* protocol (2019), we will design a primer with restriction sites at the 5' and 3' ends. The 18 nucleotides between the two restriction sites will be randomized. A complementary primer will be made to the 3' end of the randomized primer, where the random primers will be copied by extending the complementary primer using DNA polymerase. The randomized, double-stranded DNA fragments will be the binding sites for us to test. The success of PCR amplification will be checked by resolving the final product on a 10% TBE polyacrylamide gel. A test run was done, and the resulting gel is shown in Figure 4. Since the sequences will contain a high GC content, a special DNA polymerase will be used, and the PCR conditions will need to be optimized. Using the restriction sites in the primers and recipient plasmid, the resulting double-stranded fragments will serve as potential DNA binding sites by being ligated into the B1H plasmid near the promoter of a polycistronic reporter encoding the *HIS3* and *URA3* genes. Transformation efficiency will be tested prior to the full-scale library screen. A complexity of >5 x $10^8$ random binding sites is desired for successful screening. The cells from the transformation will be used to prepare plasmid DNA (library). The library will be transformed into an *E. coli* reporter strain. The reporter strain is described above in the Preliminary Data section. Briefly, since the reporter strain lacks the bacterial homologs of the *HIS3* and *URA3* genes, cells that will grow on 3AT containing plates but not on 5FOA medium will represent RAP1 bound to DNA site.

**Year End Progress Summary:**

**Specific Aim 1. Determine RAP1 binding using EMSA**.
Our EMSA kit we are using for our experiment uses chemiluminescence rather than radioactivity for detection. This is quite important because we are training master's and medical students in research through our projects. The positive control for the experiment is to show that TRF2, a component of shelterin complex, can bind to telomere sequences in our EMSA. TRF2 is known to bind to two copies of telomere sequences directly. We used published sequences as the binding sequences for TRF2. We used whole cell extracts and nuclear extracts from two human cell lines and purified recombinant protein expressed in E. coli. We tried a dozen different conditions, yet we were not able to show the binding of TRF2 to telomere sequences. Since then, we re-designed the target binding sequences yet again, and just recently we were able to show TRF2 binding, allowing us to continue with the project.

**Specific Aim 2. RAP1 binding sites library construction and screening**.
The construction of a DNA binding site library is still underway. The original bacterial 1-hybrid protocol from Meng *et al.* calls for specific restriction cloning sites to be utilized. We followed the

protocol precisely, but both cloning of randomized nucleotides and the library complexity were subpar. Since then, we have constructed numerous vectors with different cloning sites for the randomized oligos. We are continuing with the transformation of the potential DNA binding sites to generate a library of appropriate complexity.

We have progressed past the stage of troubleshooting for both aims in this project. We anticipate that we will have data in the next few months for specific aim 1. Specific aim 2 may take longer, but everything is set for us to proceed.

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Elucidating a Mechanistic Link Between Progranulin and Lysosomal Function in Alzheimer's 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: Assess relative roles of lysosomal function & PGRN in promoting M1 microglial inflammation.

A. Measure pro-inflammatory cytokines after alterations in lysosomal pH
B. Measure pro-inflammatory cytokines after alterations in PGRN
C. Measure ability of treatments to reduce pro-inflammatory cytokines after IFNγ treatment

Aim 2: Lysosome-PGRN Axis & M1 polarized microglia in brain tissue from Alzheimer patients.

**Background and Significance:**

New therapies targeting the early stages of Alzheimer's disease (AD) are needed to preserve cognitive function in patients. Functional alterations in progranulin (PGRN) appear early in the development of pathology, and PGRN has been shown to contribute to altered lysosomal function that is associated with early-stage AD. Thus, delineation of the mechanistic links between the lysosome, PGRN, and inflammation is needed before their impacts on neurodegeneration in AD can be understood. The evidence suggesting that both PGRN and lysosomal function play a role in the sustained neuroinflammation downstream of M1 activated microglia is two-fold. Different levels of PGRN are produced following M1/M2 polarization of microglia and lysosomal function may influence polarization of microglia to the pro-inflammatory M1 or the anti-inflammatory M2 phenotype. Understanding the link between lysosomal function and PGRN to reduce M1 polarization of microglia offers a targeted approach to abrogate pathological neuroinflammation associated with early-stage AD. The overarching goal of this work is to explore the mechanisms which establish the lysosome-PGRN-inflammation axis in AD to determine whether therapeutic approaches aimed at lysosomal pH or PGRN restoration show more promise in preventing neuroinflammation. Defining how lysosomal function and/or PGRN promotes inflammation in multiple contexts will further the preclinical development of early intervention for treatment of AD patients.

**Preliminary Data, Experimental Design and Methods:**

Aim 1 includes an assessment of cytokine and PGRN production, PGRN processing, M1 polarization, and lysosomal function assays. Levels of pro-inflammatory cytokines will be measured using both flow cytometry and multiplex cytokine assays. Changes in M1 morphology will be assessed using immunofluorescent staining for M1 markers. PGRN production and processing will be measured using ELISA and potential proteolytic processing will be assessed by performing immunoblots using GRN-specific antibodies. Two lysosomal function assays will be performed: lysosomal protease activity assays (fluorescently quenched casein particles and/or fluorescent peptides specific for cathepsins) and lysosomal pH measurement using DND-160, a ratiometric lysosomal dye which accurately measures lysosomal pH in living cells. For Aim 2, AD brain tissue will be compared to normal brain tissue by IHC using antibodies for lysosomal function (e.g. cathepsins, CD68 (a marker for mature lysosomes), and LAMP1), PGRN (GRN specific

antibodies), AD (e.g. β-amyloid, p-Tau, pTDP43), and M1 microglial polarization (e.g. MHC-II, CD80, and CD86).

**Proposed One-Year and Long-Term Outcomes:**

Submission of a NIH R15 AREA grant will be submitted in October 2023 or February 2024 to ensure funding for continuation of this project. Results will establish mechanistic details of the lysosome-PGRN-inflammation axis and, by focusing on reduction in pro-inflammatory cytokine production, provide a sound basis for development of targeted therapies to intervene early in the development of AD. Defining how the lysosome-PGRN axis promotes inflammation in multiple contexts will further the preclinical development of early intervention for treatment of AD patients.

**Year End Progress Summary:**

Aim 1: Assess relative roles of lysosomal function & PGRN in promoting M1 microglial inflammation.

We first established our ability to induce a pro-inflammatory (M1) or an anti-inflammatory (M2) phenotype in the human HMC3 microglial cell line after treatment with IFN-γ or an anti-inflammatory cytokine cocktail (IL-4, IL-10, TGF-β1, and TGF-β2) respectively. Changes in expression of several M1 and M2 markers were assessed by qPCR and observed alterations in the expression of selected markers were verified at the protein level by flow cytometry and immunofluorescent microscopy.

After polarization, we measured changes in levels of secreted modulatory cytokines to assess the response of HMC3 cells to the treatments outlined in Parts 1A, 1B and 1C below. Specifically, alteration in the pro-inflammatory phenotype was assessed by changes in IL-1β, a potent pro-inflammatory cytokine secreted by microglia that potentiates many immune responses. Alterations in IL-10 levels was used to assess dampening of a pro-inflammatory response as this cytokine is a major anti-inflammatory cytokine which limits damage to tissues during an inflammatory response. Future experiments may extend our findings to additional pro-inflammatory cytokines and markers of microglial activation. We have altered lysosomal function using two approaches: an alkalizing agent (hydroxychloroquine) to increase lysosomal pH and a broad-spectrum protease inhibitor (leupeptin) to inhibit the function of lysosomal proteases. Future experiments may involve additional treatments to target lysosomal function.

*Part 1A: Measure pro-inflammatory cytokines after alterations in lysosomal pH*

Our data suggest that compromising lysosomal function by treatment with either an alkalizing agent (hydroxychloroquine) or a broad-spectrum protease inhibitor (leupeptin) increases secretion of IL-1β in the HMC3 cell line when compared to control as measured by flow cytometry. Interestingly, treatment with IFN-γ alkalizes lysosomal pH to a level comparable to treatment with hydroxychloroquine. Future experiments will extend these findings to include other pro-inflammatory cytokines and pro-inflammatory markers utilizing additional disruptors of lysosomal function.

*Part 1B: Measure pro-inflammatory cytokines after alterations in PGRN*

The literature suggests that PGRN has an anti-inflammatory, neuroprotective function in the context of PGRN deficiency. Consistent with this finding, we observed a dose-dependent increase in IL-10 production with an increase in PGRN levels in HMC3 cells. However, we have also documented an unexpected increase in IL-1β in response to treatment with increasing amounts of exogenous PGRN measured by flow cytometry in HMC3 cells.

*Part 1C: Measure ability of treatments to reduce pro-inflammatory cytokines after IFNγ treatment*
Primary mouse microglial cells were treated with PGRN, IFN-γ, or both in combination. Results suggest that PGRN alone increases expression of the M2 marker CD206 as measured by immunofluorescent microscopy. Interesting, the combination of PGRN and IFN-γ increased expression of the M1 marker to similar levels as treatment with IFN-γ alone.

Taken together, the data from Parts 1B and 1C suggest that response to PGRN treatment may depend on other inflammatory signals. As these unexpected results extend to two experimental models, future aims will be focused on delineating this context-dependent response to PGRN treatment as this will be foundational for the development of PGRNs potential as a therapeutic.

Aim 2: Lysosome-PGRN axis & M1 polarized microglia in brain tissue from Alzheimer patients.

We have tested antibodies for several lysosomal markers including the lysosomal biogenesis marker BLOC1S1 and C1qA to initiate these studies, as data obtained as part of our Midwestern-Arizona Alzheimer Consortium grant shows that C1q levels increase in dysfunctional lysosomes as part of formation of the pro-inflammatory complosome complex. Thus, as C1q is a marker of both inflammation and dysfunctional lysosomes, initial experiments have focused on localizing C1q in AD patient tissue. Preliminary results suggest that C1q levels increase in AD patient samples compared to control, and correlations with β-amyloid plaque levels are underway. Future experiments will compare these findings to other markers of lysosomal dysfunction and AD disease including cathepsins and p-Tau. These data will be used to assess the number of patient samples needed to be included as part of a larger study in the upcoming year.

# ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Progranulin Transport & Processing: Implications for Development of New Alzheimer's Therapies.** 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: Receptor-mediated cellular uptake of labeled PGRN
Aim 2: Localization and lysosomal processing of labeled PGRN
Aim 3: Assessment of lysosomal function after addition of PGRN

**Background and Significance:**

New therapies targeting the early stages of Alzheimer's disease (AD) are needed to preserve cognitive function in patients. Functional alterations in progranulin (PGRN) appear early in the development of pathology, and PGRN has been shown to contribute to altered lysosomal function that is associated with early-stage AD. Thus, delineation of the mechanistic links between the lysosome, PGRN, and inflammation is needed before their impacts on neurodegeneration in AD can be understood. This project focused on improving our understanding of the mechanism of PGRN transport and processing required for effective development of therapeutics. While a link between lysosomal dysfunction due to PGRN loss has been established, no studies to date have detailed the mechanisms by which PGRN promotes lysosomal function. Additionally, recent data suggest that PGRN may be targeted to the lysosome for disposal, impacting development of pathology. The premise of this work is that correct transport to and processing in the lysosome is necessary for the maintenance of lysosomal function in healthy cells. Work proposed delineates the mechanism by which this occurs and, time permitting, addresses how the normal physiology is disrupted with inflammatory signaling leading to disease. Our hypothesis is that lysosomal processing of PGRN to GRN constituents is necessary to maintain lysosomal function and that LRP1/M6PR is more effective in the delivery of PGRN to the lysosome. The overall objective is to delineate how PGRN contributes to lysosomal function in order to facilitate the development of PGRN-based therapeutics.

**Preliminary Data, Experimental Design and Methods:**

Biotinylated human recombinant PGRN will be added to human microglial cells (HMC3 cells). Immunoblot analysis using anti-PGRN and streptavidin labeled antibodies will be performed to determine the amount of exogenous PGRN was internalized into the cells and compared with untreated cells. shRNA plasmids targeting SORT1, PSAP, and LRP1/M6PR will be transfected into HMC3 cells, incubated with biotinylated human recombinant PGRN and the amount of labeled PGRN internalized will be assessed. Lysosomal protease activity will be measured using fluorescent microscopy in control, PGRN treated, and shRNA knock-down HMC3 cells. Our lab has been successful in performing density gradient isolation of lysosomes. Lysosomes will be isolated from control and treated cells and the amount/fraction of labeled PGRN that localized to the lysosome will be compared to the total intracellular labeled PGRN, and lysosomal protease activity will be measured using commercially available FRET peptides specific for identified lysosomal proteases. In addition, processing of PGRN to GRN subunit(s) in the lysosomal fraction will be assessed by immunoblotting using anti-GRN specific antibodies.

**Proposed One-Year and Long-Term Outcomes:**

We anticipate that the completion of these aims will provide preliminary data for the submission of an R15 grant near the conclusion of the funding period. In addition, we expect that these data will be combined with existing data utilizing the SW13 cell line for a publication in the near future. Future directions will include the development of more rapid screens for the impact of PGRN treatments on the pH of cells and a focus on primary neuronal cultures, including neurons, astrocytes, and microglia. In combination, these studies will provide a solid foundation for the development of new therapeutics for early intervention in AD patients.

**Year End Progress Summary:**

Progress was made on two of the three aims. Specific progress, challenges encountered, and ongoing experiments are summarized below by Specific Aim.

*Aim 1: Receptor-mediated cellular uptake of labeled PGRN*

Initial experiments to determine the amount of endogenously-synthesized PGRN that is produced by HMC3 cells were performed; results showed that PGRN is highly expressed in HMC3 cells, which we determined would hinder our ability to accurately quantify the proportion of intracellular vs exogenously added PGRN in cellular lysates and/or lysosomes and have altered our approach. To avoid issues involved with transfection of multiple shRNA plasmids, we will complete these experiments utilizing a *GRN* knock-out in HMC3 cells. We have begun the process of generating a CRISPR-Cas 9 knockout out the *GRN* gene and will use this line to define the roles pf SORT1, PSAP, and LRP1/M6PR using shRNA approaches and labeled exogenous PGRN.

*Aim 2: Localization and lysosomal processing of labeled PGRN*

To begin this aim, we focused on SW13 cells as these cells exist in two epigenetically distinct subtypes (SW13+ and SW13-) that have differences in lysosomal pH and PGRN production. We have successfully isolated lysosomes and sent the lysosomal fractions from each subtype for proteomic and lipidomic analysis. Our results show that there are changes in gene expression in markers of lysosomal function (e.g., LAMP1), PGRN metabolism (e.g., PSAP and LRP1), and inflammation (e.g., IL-6 and C1q). Lysosomal fractions from HMC3 cells and PGRN knock-out HMC3 cells will be sent for proteomic and lipodomic analyses in parallel after completion of the CRISPR-Cas9 knockout. To address the link between lysosomal function and inflammation, we showed that inhibition of lysosomal function in HMC3 cells with leupeptin (a broad-spectrum protease inhibitor) or hydroxychloroquine, (a lysosomal alkalizer) results in an increase in IL-1β expression. Furthermore, treatment with the pro-inflammatory cytokine IFN-γ resulted in a decrease in lysosomal pH. These results will serve as the foundation for PGRN supplementation experiments which will be completed once the PGRN knock-out cell line is available for use.

*Aim 3: Assessment of lysosomal function after addition of PGRN*

With the goal of determining PGRN's effect on lysosomal function and related inflammation, we initially established that the addition of IFN-γ induces polarization of HMC3 cells to the M1 phenotype. We then showed by qPCR that treatment of HMC3 cells with IFN-γ results in an increase in expression of various M1-microglial markers: CIITA (Class II MHC transcription factor), CD68 (macrophage lysosomal marker upregulated in inflammation), and IL-1β (pro-inflammatory cytokine). For this aim, we hypothesized that PGRN would be neuroprotective and reduce M1 polarization, thus dampening inflammation. Surprisingly, the addition of PGRN resulted in a significant increase in the proportion of HMC3 cells expressing M1 cytokines (IL-1β

and IL-6) but also resulted in an increase in an M2 cytokine (IL-10), as measured by flow cytometry. This was a modified experimental protocol than originally proposed, but the acquisition of a new flow cytometer on campus allowed for these experiments to be performed. As these were unexpected results, we then performed an additional experiment where unpolarized HMC3 cells were pre-treated with PGRN, then challenged with either M1- or M2-polarizing cytokines. Interestingly, we found that PGRN pre-treatment resulted in a decrease in IL-1β expression and enhances mRNA expression of STAT6, a transcription factor associated with an anti-inflammatory M2-microglial phenotype. Thus, we conclude that PGRN treatment alone, once an M1-mediated inflammatory response was initiated, was not protective but pre-treatment of the cells with PGRN prior to the initiation of M1-mediated inflammation was protective. While preliminary, these results suggest that PGRN may be neuroprotective prior to onset of disease symptoms, or at least early in the disease course, which would support the development of therapeutics can slow or halt disease progression if used earlier in the disease stage. As lysosomal function is linked to neuroinflammation, our results suggest that lysosomal function would be reduced. We are in the process of performing lysosomal protease activity assays on cells treated with PGRN and anticipate we will have results on these experiments later this calendar year.

# ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Evaluation of Regional Differences in Bacterial DNA Presence in the Brain Tissue of Alzheimer's Disease Patients and Controls.** Garilyn Jentarra, PhD, T. Bucky Jones, PhD, Keehoon Lee, PhD, Haiwei Gu, PhD. Midwestern University; Translational Genomics Research Institute; Arizona State University; Arizona Alzheimer's Consortium.

**Specific Aims:**

We propose to expand previous metagenomic analysis of DNA extracted from Alzheimer's disease and control brain tissues on substantially larger subject groups to validate and extend findings.

Aim 1.1: Extract and purify DNA from post-mortem brain tissue samples. Send the extracted DNA for 16S rRNA gene sequencing at a commercial laboratory. Returned metagenomic data will be used for the analysis described in Aims 1.2 and 1.3.

Aim 1.2: Assess brain regional differences using metagenomic analysis of taxonomic data provided by 16S rRNA gene sequencing.

Aim 1.3: Assess between-group differences using metagenomic analysis of taxonomic data provided by 16S rRNA gene sequencing.

**Background and Significance:**

Despite intensive research, the trigger for the pathology of Alzheimer's disease remains unknown. There have been repeated suggestions in the literature that infection with various microbes[1,2], including bacteria[3,4], viruses[5-7], and fungi[8-10], could play a role in the development of AD pathology[11]. Recent data also indicates that the amyloid-beta peptide ($A\beta_{(1\text{-}40 \text{ or } 1\text{-}42)}$), which aggregates to create the hallmark amyloid plaques of AD, is in fact a very strong anti-microbial peptide[12-14]. Given our preliminary data (below), and data published by others, there is good reason for the brain to produce an anti-microbial peptide as part of an innate defense system, and this supports the idea that microbes may be involved in AD. Hyperphosphorylation of tau protein, leading to the characteristic neurofibrillary tangles of AD, can also be induced by both viral and bacterial infection[15-17]. Intracellular and plaque-localized LPS has been described in AD brain tissue[18], and we were able to detect it in our own experiments.

Along with descriptions of microbes in AD brain tissue, the scientific literature also contains a large body of work describing the chronic immunological responses typical of AD. Microglial activation and cytokine production have been widely described in AD, and have been characterized as inflammatory[19-22]. There are suggestions that systemic inflammation during middle age also correlates with later cognitive decline[23]. The complement system is activated in AD brain tissue[24] although, again, the reason for this has been unclear. In addition, many acute phase reactants, commonly produced by the liver as part of an innate response to infection, are found in increased levels in AD brain tissue. This includes C-reactive protein (CRP)[25-26], fibrinogen/fibrin (blood clotting and innate immunity)[27-29], and serum amyloid A (SAA)[30].

Collectively, these findings, combined with our own, provide reason to continue to explore the potential role of microbes in the pathology of Alzheimer's disease. Below, we describe some of our key findings that support the continuation of this exploration and the experimental plan that will allow us to assess the functional relevance of data more thoroughly in terms of the etiology of Alzheimer's disease.

**Preliminary Data, Experimental Design and Methods:**

We previously performed metagenomic analysis of DNA extracted from the post-mortem brain tissue of small groups (n=12 each) of Alzheimer's disease patients, as well as individuals with mild cognitive impairment (MCI, possible early-stage), high pathology controls (tissue pathology but no dementia), and non-demented normal control subjects. The analysis was conducted on matched tissue samples from both the superior frontal gyrus (SFG) and the inferior temporal gyrus (ITG) of the same subjects, which allowed us to assess regional differences in bacterial DNA presence in addition to between-group differences. While we identified strong regional differences in bacterial DNA, high variability between subjects, even within the same groups, made detection of between-group variability very difficult. Proteobacteria was the major phyla in the SFG for all subject groups, overall comprising ~50% of the bacteria detected in each group on average. In the ITG, all subject groups are also dominated by the presence of proteobacteria, but with an average proportion of around 75% in each subject group. Also notable is a dramatic difference in the abundance of Firmicutes phylum bacteria in the SFG (~14-34%) versus the ITG (~6-10%). However, between-group differences within the SFG or ITG were non-significant, which might be due to very high variability between subjects within groups.

Principal components analysis verified the significant regional differences in predominant bacteria phyla, in particular showing that the SFG and ITG could be distinguished by the presence of Proteobacteria versus Firmicutes bacteria. An additional PCA analysis showed the Proteobacteria group differed substantially between the two tissues, with ITG dominated by Gammaproteobacteria and SFG dominated by Bacilli, which is further evidence of differences in microbial content between the brain regions. This is relevant for two reasons. First, the ITG is affected earlier and more prominently by tau-associated AD pathology than the SFG, suggesting a fundamental difference in the disease process. Second, while both the nasal cavity and a compromised blood-brain-barrier (a consequence of aging) are viable entry points into the brain, neuronal pathways more closely connect entry of microbes through the nasal cavity to the ITG. Thus, while both regions may be susceptible to bacterial entry through the blood brain barrier, bacteria found in the ITG may additionally be entering through the nasal cavity, which is a known entry point for microbes into the brain[31]. The average amount of lipopolysaccharide (LPS), a component of the gram-negative bacterial cell wall, was also measured in the two brain regions. Statistically significant regional differences in LPS and LTA were identified. Those differences closely aligned with the relative abundance of gram-negative to gram-positive bacteria found via sequencing.

Tissue Acquisition: As a consequence of the work done in the NIH R21 awarded to Dr. Jentarra, we have already acquired an additional 160 subject tissues (40/subject group) from the SFG and will soon acquire an additional 160 ITG tissues from the same subjects. While the R21 work is not focused on microbes, there is sufficient extra tissue for use in the experiments proposed here, which are allowed under the material transfer agreement (MTA) used to acquire the tissues. We therefore do not require funding for the purchase of tissues, but do require funding to cover DNA extraction, purification, and sequencing.

Aim 1.1: DNA extraction and purification: Brain tissue will be sterilely subsampled from each tissue sample. DNA extraction will be performed on 100 mg of each tissue under sterile, DNA-free conditions using the Qiagen Powersoil DNA Isolation Kit. The NEBNext Microbiome DNA Enrichment kit will then be used to remove most of the methylated mouse genomic DNA in each sample, to allow for more accurate metagenomic sequencing. Analysis for the presence of bacterial DNA will be performed by a commercial sequencing laboratory. The 16S rRNA gene

sequencing protocol involves amplicon production and creation of tagged libraries of DNA fragments. Primers targeting the V4 region of the 16S rRNA genes are as published by Caporaso *et al* [32]. Samples will be analyzed using the Illumina MiSeq platform. During analysis, sequences will be clustered against a bacterial database for identification. Sequences information will be reported to us as both the absolute number of reads and the percentage of total reads for each sample. Due to the nature of this type of sequencing, read number is not reliably quantitative but the analysis does provide solid information regarding number and identity of different types of bacteria. Removal of Contaminating Microbial Sequences: A known problem in sequencing of low microbial abundance samples is the inherent contamination of commercial kits and reagents with low levels of microbial DNA. A background control (no tissue) will be run with all sample sets to identify contaminating sequences. This control will begin in our laboratory during the DNA extraction process and extend through the final sequencing.

Aim 1.2: Analysis of Brain Regional Differences: After the sequencing data is returned to us, we will analyze the differences in relative abundance of taxa between the SFG and ITG, as shown in our Preliminary Data. While analysis at the phylum level was shown in this proposal, we will perform the analysis at lower taxonomic levels. This analysis (including statistics) will be performed using the QIIME2 software, which is designed specifically for metagenomic analysis of microbial communities.

Aim 1.3: Analysis of Between-Group Differences: Measures of alpha and beta diversity will be performed using the QIIME2 software, as well as analysis of differences in relative abundance of bacterial taxa between our subject groups. We will analyze the data at all taxonomic levels to assess both broad differences and more subtle differences in the microbial communities found in our subject groups.

**Proposed One-Year and Long-Term Outcomes:**

We are currently in the process of publishing the original data from the smaller subject groups. That paper will focus on the regional differences we discovered. Once we have obtained expanded data from this much larger set of subjects, we will prepare that for publication as well. Our intention is to use both the original and expanded data to apply for an NIH R15 grant to support our ongoing research in this area. Because of increasing interest in the relationship of microbes to Alzheimer's, the National Institute on Aging has issued a Notice of Special Interest (NOSI) for studies related to an "Infectious Etiology of Alzheimer's Disease". Our research fits well in their list of appropriate research topics.

**Year End Progress Summary:**

As planned, the necessary 160 samples of temporal gyrus tissues were acquired from BSHRI. These samples are from the same subjects from whom we previously acquired 160 samples of superior frontal gyrus. We now have samples from two different brain regions for each of our subjects. Note that while we had proposed obtaining inferior temporal gyrus, sufficient tissue for many subjects for that brain area was no longer available. In consultation with BSHRI, we chose to use tissue from the adjacent medial temporal gyrus. Using the methods we have developed in our lab, we removed contaminating DNA that may have existed on the surface of the tissue. We then carefully performed DNA extractions on all 320 samples under sterile conditions to minimize contamination with exogenous DNA sequences. Following DNA extraction, we processed each sample with the NEBNext Microbiome DNA Enrichment Kit to remove methylated human DNA. Subsequently, we sent the DNA samples to TGen for 16S rRNA gene sequencing, using their methods for analysis of low microbial-biomass tissues. We are currently awaiting the final

sequencing data and preliminary data analysis that will be provided by TGen for these samples. We have met with Keehoon Lee from TGen, who has offered to collaborate with us in the broader analysis of these samples. While waiting for the new data, we have completed a substantial manuscript describing our original experiments, which provided the preliminary data for this proposal. This manuscript was just accepted for publication in the journal *Brain Sciences*. We will use this publication and new data from the current study as the basis for an NIH R15 REAP or R21 grant proposal to further extend this work.

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Geroscience Approach to Alzheimer's Disease: Mitigation of Cellular Senescence by Intermittent Fasting.** Minsub Shim, PhD, Layla Al-Nakkash, PhD, Thomas Broderick, PhD.
College of Graduate Studies, Midwestern University; Arizona Alzheimer's Consortium.

**Specific Aims:**

Senescence Accelerated Mouse-Prone 8 (SAMP8) mice are a sub-strain of senescence-accelerated mice (SAM). They are characterized by an early manifestation of age-related phenotypes, including age-related deficits in learning and memory. We found intermittent fasting improved memory function and reduced senescence in aged SAMP8 mice. We propose that decreased age-associated inflammation and subsequent improvement in insulin signaling as a mechanism underlying the beneficial effects of intermittent fasting on improved memory function in aged SAMP8 mice.

- *Specific Aim 1: To determine the role of age-associated inflammation in impaired insulin signaling and memory dysfunction in aged SAMP8 mice*
  Specific Aim 1 will test our hypothesis that a decreased level of senescence would reduce inflammation in aged SAMP8 mice. Memory function and the levels of senescence markers in the tissues of SAMP8 mice fed either a control or an aspirin-containing diet will be analyzed by various methods.
- *Specific Aim 2: To identify an improved insulin signaling as a mediator of enhanced memory function in aged SAMP8 mice subjected to intermittent fasting*
  In Specific Aim 2, we will determine the effect of metformin on the memory/learning function of aged SAMP8 mice to analyze the direct association between peripheral insulin resistance and brain aging/progression of AD.

The research conducted during this funding period was an extension of the previous project, which would provide mechanistic insight into the beneficial effects of intermittent fasting against brain aging, which we discovered in the last funding period.

**Background and Significance:**

Alzheimer‘s disease (AD) is a progressive, degenerative disorder of the brain and is the most common form of dementia in older adults. The onset of AD is insidious, and the disease manifests clinically as progressive memory impairment and cognitive decline. According to the World Alzheimer's Report 2021, more than 55 million people worldwide suffer from dementia, and this number is predicted to reach 78 million by 2030 and 152.8 million by 2050.

Since aging is a critical risk factor in various human pathologies, including AD, determining the causal cellular and molecular processes that lead to functional decline and frailty is crucial for achieving the goal of “healthy aging”.

While the causes of aging or age-related diseases remain elusive, increasing evidence supports the connection between cellular senescence and organismal aging. The senescent cells secrete inflammatory cytokines and extracellular proteases, known as senescence-associated secretory phenotype (SASP), that are linked to chronic inflammation and disruption of tissue function.

AD is conventionally regarded as a disease that selectively affects certain regions of the brain. However, recent reports indicate that AD is also linked to peripheral and systemic abnormalities, suggesting that age-related changes in non-neuronal tissues may contribute to the development

and progression of AD. For example, impaired insulin signaling has been suggested to play an important role in the development and progress of AD.

In the previous funding period, we found that intermittent fasting results in (i) decreased levels of SASP and (ii) improved glucose metabolism and memory function in aged SAMP8 mice.

Based on our preliminary data, we proposed to test a hypothesis that the beneficial effects of intermittent fasting result from the suppression of cellular senescence in peripheral tissues. Given the strong association between insulin resistance and AD, we further hypothesized intermittent fasting delays AD progression by suppressing the accumulation of senescent cells, resulting in reduced inflammation and subsequent improvement in insulin signaling.

**Preliminary Data, Experimental Design and Methods:**

Forty-eight SAMP8 mice were used in this study (8 males and 8 females/group, 3 groups: control diet vs. aspirin diet vs. metformin diet). Dyets, Inc. prepared the custom diet containing aspirin and metformin. Control diet-fed mice were shared between Specific Aims 1 and 2. SAMP8 mice for the experiment were generated from our breeding colony. The animals were provided *ad libitum* access to water and a standard laboratory diet until 3 months of age. Three-month-old SAMP8 mice were randomly assigned to three differentially fed groups as described above. Because this study involves feeding mice with an aspirin- or a metformin-containing diet to determine the impact of reduced inflammation and improved insulin signaling on memory function, the animals were not subjected to intermittent fasting. Instead, the mice had *ad libitum* access to a control or a drug-containing diet. At the age of 8 months, the learning and memory functions of the control and treatment groups were tested. Additionally, a glucose tolerance test was conducted. At the termination of the feeding experiment, 8-month-old mice were sacrificed, and various tissues were harvested.

**Proposed One-Year and Long-Term Outcomes:**

To our knowledge, this is one of the few studies investigating the long-term effects of intermittent fasting on aging using a mouse model of early aging. This study will further determine the mechanism underlying the beneficial effects of intermittent fasting on brain aging and/or pathology of AD. This study resulted in the development of collaborative studies with Drs. Layla Al-Nakkash and Thomas Broderick (Department of Physiology, College of Graduate Studies, Midwestern University). Three medical students are currently working on this project as part of their summer research program. The findings from this study will be presented at Kenneth A. Suarez Research Day at MWU and the 2024 Arizona Alzheimer's Consortium Annual Scientific Conference. We plan to submit a manuscript this fall. We also plan to submit an NIH proposal focusing on "*Geroscience approaches to AD*" and/or "*metabolic changes in AD*".

**Year End Progress Summary:**

- Specific aims 1 & 2
  The SAMP8 mice were fed an aspirin- or metformin-containing diet for 5 months. We did not observe any pathologies in aspirin- and metformin-fed mice. The mice also gained normal weight. We conducted a Y-maze analysis and found that aspirin- and metformin-fed mice have a better memory function than control diet-fed mice. Additionally, we found that aspirin and metformin improved glucose control in aged SAMP8 mice while the control diet-fed group exhibited an impaired glucose tolerance, a sign of insulin resistance. Furthermore, the molecular analysis identified that aspirin and metformin reduced the levels of senescence markers in the fat tissue of the aged SAMP8 mice. Molecular and histopathological analysis

of other tissues, including skeletal muscle, liver, and pancreas, is in progress. We are currently analyzing the brain tissues of SAMP8 mice for signs of neuronal degeneration.

Given that one of the hallmarks of aging is the accumulation of senescent cells, our findings suggest a possible relationship between cellular senescence, insulin resistance, and impaired memory function. As previously mentioned, this is one of the few studies investigating the long-term effects of intermittent fasting on aging using a mouse model of early aging. We plan to submit a manuscript on our novel findings this fall.

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Determining the Molecular Mechanism of γ-Secretase Activation by the Telomere Protein RAP1.** Mark J. Swanson, PhD (PI), Nancy S. Bae, PhD (Co-I). College of Graduate Studies, Midwestern University; Arizona Alzheimer's Consortium.

**Specific Aims:**

Specific aim 1. Determine if RAP1 is a general γ-secretase activator or a specificity factor.

Specific aim 2. Determine how the PS1 and RAP1 interaction affects the activity of γ-secretase.

**Background and Significance:**

The deposition of amyloid peptides in senile plaques is a hallmark of Alzheimer's disease (AD). Early-onset AD (EOAD) is primarily caused by mutations in one of three genes: *APP*, *PSEN1* or *PSEN2*. The *APP* gene encodes the amyloid precursor protein, which has a transmembrane domain embedded in the plasma membrane of the cell. β-secretase is an enzyme that cleaves APP, producing a fragment of the protein made up of the carboxyl(C)-terminal 99 amino acids, called C99, that is embedded in the plasma membrane. γ-secretase is a multi-subunit protein complex. It contains a catalytic subunit, either presenilin 1 or 2 proteins (PS1 or PS2, encoded by the *PSEN1* and *PSEN2* genes, respectively). Three non-enzymatic subunits are required for activity: Anterior Pharynx-1 (Aph-1), Nicastrin (Nic) and presenilin enhancer 2 (Pen2). γ-secretase cleaves C99 within the membrane spanning portion, producing amino(N)-terminal Aβ peptides released outside of the cell and the C-terminal amyloid precursor protein intracellular domain (AICD), which enters the nucleus to affect gene expression. Most Aβ peptides produced are 40 amino acids in length (Aβ40) and are soluble. The less soluble Aβ42 peptides are less frequently made. When the ratio of Aβ40:42 favors the more soluble Aβ40, the brain functions without AD-related pathology. Higher levels of Aβ42 promote self-aggregation resulting in the formation of senile plaques. Due to its ability to form amyloid peptides, γ-secretase has been a target for therapeutic intervention, but small molecule inhibitors have not been successful since they affect γ-secretase processing many of its 149 target proteins, resulting in worsening of patient outcomes. Alternatively, regulation of γ-secretase is being explored through proteins that modulate its activity. Previously, four γ-secretase modulatory proteins (GSMPs) were identified through their interaction with γ-secretase. Recently, our lab identified a telomere protection protein, RAP1 (TERF2IP), as the newest GSMP since it increased γ-secretase activity.

**Preliminary Data:**

Our lab found that the N-terminal, cytoplasmic domain of PS1 (amino acids 1-85; $PS1_{(1-85)}$) interacts with RAP1. We tested the effect of RAP1 on γ-secretase using our lab's reconstituted γ-secretase system in yeast. PS1 was chosen as the catalytic subunit as most EOAD mutations occur in *PSEN1*. Our target gene for γ-secretase activity was a fusion of C99 and the yeast GAL4 transcriptional activator (C99-GAL4). When C99-GAL4 is expressed in yeast, C99 is embedded in the plasma membrane, trapping GAL4 at the cellular periphery. When γ-secretase is active, C99 is cleaved, and GAL4 is released from the membrane, enters the nucleus and activates genes. We tested γ-secretase activity using this system and an enzyme-producing reporter gene. RAP1 caused a 10-fold increase in reporter activity compared to a control strain. Supporting this, RAP1 overexpression in human glioblastoma cells led to an increase in amyloid beta peptide production (1.7-fold for Aβ40 and 1.3-fold for Aβ42).

**Methods/Experimental Plans:**

***Specific Aim 1*. Determine if RAP1 acts as a general γ-secretase activator or as a specificity factor.**

Aim 1a. Though RAP1 increases the reporter enzyme activity in yeast, it is important for us to show that there is an increase in C99-GAL4 processing in these cells. We will detect C99-GAL4 by introducing a multiple-copy epitope tag, $myc_{13}$. We attempted detection of Aβ peptides in the medium using ELISA, but this was unsuccessful. Thus, we will develop a protein gel system to detect specific Aβ peptides.

Aim 1b. γ-secretase exists as multiple complexes with either PS1 or PS2 as the catalytic subunit. We showed that RAP1 interacts with PS1 and increases PS1 containing γ-secretase activity in our yeast system. We will try these experiments using PS2 to determine specificity.

Aim 1c. γ-secretase cleaves at least 149 transmembrane protein targets. Our data show that RAP1 can increase γ-secretase activity on C99 of APP. Other GSMPs affect γ-secretase activity differentially on APP versus Notch1 (another target protein). We will generate Notch1 and CDH2 (a.k.a. N-cadherin; another γ-secretase target protein) fusions with GAL4 and test the effect of RAP1 on γ-secretase activity with these targets in the yeast system.

Aim 1d. We will test whether GSMPs may alter γ-secretase activity on specific targets by binding them. We will determine if RAP1 can increase γ-secretase activity on an APP target that lacks the cytoplasmic domain (C55-GAL4) as compared to C99. We will also test *in vitro* interactions between RAP1 and the AICD fragment. RAP1 interactions with Notch1 and CDH2 will only be tested if RAP1 increases cleavage activity on these targets.

***Specific Aim 2*. Determine how the PS1 and RAP1 interaction affects the activity of γ-secretase.**

Aim 2a. We will introduce a PS1 mutation that has the first 85 amino acids deleted into the yeast system to determine the effects of the RAP1/$PS1_{(1-85)}$ interaction. We will also test the effects of AD-associated point mutations in the PS1 amino-terminus to determine their effects in the yeast system. These mutants will be tested in this system with RAP1 as well.

Aim 2b. We will determine the specific domain of interaction in RAP1 for the PS1 N-terminus. We will determine the effects of mutations of three serine residues that are known to be phosphorylated using alanine and aspartic acid substitutions. We will also determine the effects of converting the histidine residue at position 130 of human RAP1 to a leucine, which is the only difference amino acid difference between humans and non-human primates. We will use random mutagenesis of RAP1 to identify mutations that prevent RAP1 from increasing γ-secretase activity. For this to work, we will need to create an attenuated γ-secretase system in yeast. To reduce the γ-secretase of our system, we will test the use of single-copy plasmids expressing the γ-secretase subunits.

**Proposed One-Year and Long-Term Outcomes:**

**Specific Deliverables/Future Plans**

This work will provide insight into the mechanisms for the production of amyloid peptides leading to plaque formation, a hallmark of AD. If RAP1 specifically activates γ-secretase cleavage of C99, it could be a useful therapeutic target. Some of the research proposed in this application has been designed to address the concerns of reviewers of our R15 REAP application and suggestions from reviewers of our recent publication (Swanson *et al*. G3 (Bethesda), in press). One of the

main concerns from the grant reviews was that the γ-secretase complex in yeast was not stable, and the interaction with RAP1 was merely stabilizing the complex, leading to an increase in activity. The data showing PS1 auto-cleavage is a critical part of the story needed to refute the idea of stabilization. We need to show that the cleavage of C99-GAL4 is increased at the same time. The use of additional γ-secretase target proteins may show differential cleavage compared with RAP1 also indicating the complex is not merely being stabilized. The specific details of the interactions using PS1 mutations that have been linked to AD may indicate that RAP1 contributes to the pathology. If we can develop an attenuated γ-secretase system in yeast, it would allow us to screen for novel GSMPs without the need to introduce mutations in the γ-secretase subunits or APP, which is advantageous since mutations in these might preclude that identification of important regulators. Data obtained from the MAAC funded proposal of 2021-2022 was critical for our recent publication. The data obtained from the studies proposed in this application will be used as preliminary data for the resubmission of federal grants (R15 REAP to NIGMS) as well as for publications.

**Year End Progress Summary:**

***Specific Aim 1*. Determine if RAP1 acts as a general γ-secretase activator or as a specificity factor.** To attenuate the current yeast system and to accommodate a variety of γ-secretase target proteins, we are redeveloping our yeast system to express the γ-secretase subunits from the chromosome of yeast and express target proteins and GSMPs from plasmids. Doing so will also increase the sensitivity of the system. This requires us to reorganize the marker genes that we can use in this system. Due to the complexities of introducing so many human genes into the yeast, we have developed a method to allow us to recycle certain marker genes. We are generating a multifunctional yeast reporter strain. We anticipate that expressing C99-GAL4 from a plasmid may allow us to detect amyloid peptides using ELISA though we are still developing a gel system to measure them.

Expressing the different target proteins in yeast requires a signal sequence so the proteins are embedded in the plasma membrane. The signal sequence was included in the PCR primers for the targets. This worked well for C99, but it has not worked for other targets (Notch1 and CDH2). We are developing a target gene plasmid that can accommodate any target we amplify that includes the leader sequence, and it includes an epitope tag for the detection of cleaved products to verify any changes in γ-secretase activity detected by reporter gene activity.

We have cloned the five GSMPs (not just RAP1 as proposed), the PS1 and PS2 N-termini, and the AICD as fusions with affinity tags. The proteins are currently being expressed to determine interactions among them. We extended these studies to include the other GSMPs to make a complete story comparing all GSMPs to see if they function similarly (hopefully for a publication). Each GSMP will be tested to determine if they can affect γ-secretase activity using C55-GAL4 (lacking the AICD) in the yeast system. We are also working to test interactions and effects using Notch1 and CDH2.

***Specific Aim 2*. Determine how the PS1 and RAP1 interaction affects the activity of γ-secretase.** AD-associated point mutations in the N-terminus of PS1 have been created and are being tested for interaction with RAP1 using *E. coli* expressed proteins. The PS1 deletion of the amino-terminus has been difficult to clone due to the inclusion of a signal sequence for PCR, so we are modifying our target gene plasmid by removing GAL4 to allow the expression and proper membrane insertion of the N-terminally truncated PS1. A PS2 N-terminal deletion is also being generated.

Plasmids for the expression of RAP1 domains as GST-fusion proteins have been made and are being used to determine the interaction with PS1. The serine residue mutations have been made and are ready to test for interactions. They have also been cloned into the plasmid for testing in the yeast γ-secretase system. The RAP1 H130L mutation has been made, and it did not alter γ-secretase activity in the current yeast system, but we will test it in our new system once it is ready.

Overall, cloning, mutagenesis, plasmid vector creation, and yeast strain creation have been done, and some cloning remains. We are currently testing interactions and transforming yeast for activity assays. We anticipate obtaining data from these experiments over the next few month

# NORTHERN ARIZONA UNIVERSITY
# PROJECT PROGRESS REPORTS

# ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**A Comprehensive Analysis of the Gut Microbiome in Alzheimer's Disease: Insights From Murine and Human Studies.** Emily K. Cope, PhD, J. Gregory Caporaso, PhD, Tinna Traustadòttir, PhD, Jonathan Lifshitz, PhD, Carol Barnes, PhD. Northern Arizona University; Barrow Neurological Institute at Phoenix Children's Hospital; University of Arizona College of Medicine-Phoenix; Phoenix VA Health Care System; University of Arizona; Arizona Alzheimer's Consortium.

**Project Description:**

The gut microbiome-brain axis, or the bidirectional communication between the microbiota that colonize the GI tract and the brain, is highly relevant in Alzheimer's disease (AD). We have demonstrated that gut microbiota composition can predict individuals predisposed to develop AD in a 3xTg-AD mouse model prior to onset of pathologies. Further, we have demonstrated that certain microbial taxa, including *B. fragilis*, are enriched after development of amyloid-β plaques. In this project, we contextualized our findings in 3xTg-AD and APPSEN1 murine models of AD pathologies by performing a comprehensive pooled analysis on publicly available AD human and AD mouse model microbiome sequence data. We performed neuropathological and cognitive assessments to associate gut microbial features with AD pathologies and cognitive function. Finally, in an effort to understand the role of the microbiome in aging and AD, we began to study the gut microbiome composition and function before and after an intervention with a phytonutrient and exercise in a cohort of aging individuals.

**Specific Aims:**

To further understand the role of the microbiome in aging and Alzheimer's Disease, we propose the following Specific Aims:

Specific Aim 1. We will identify patterns of microbial community structure in a pooled analysis of data generated from our prior studies in 3xTg-AD mice in the context of published data in mice modeling AD pathologies, data from human cohorts of patients with AD, and healthy controls.

Specific Aim 2. Tests the association of microbial community members with neuropathological and behavioral outcomes in 3xTg-AD mice challenged with the neurotrophic bacterium, *B. fragilis,* or a vehicle control.

Specific Aim 3. Tests the effect of sulforaphane (SFN), a phytonutrient that improves redox balance and cell signaling response to oxidants, and exercise on the gut microbiome in a cohort of aging individuals.

**Background and Significance:**

The gut microbiota-brain axis is the bidirectional communication between the gut and brain through immune, nervous, metabolic, and endocrine signaling.[1] These collective mechanisms regulate a number of physiological processes, including gut motility and permeability[2], and inflammation at extragastric sites, such as the brain.[34] In our prior studies supported by the AAC, we observed a marked increase in *Bacteroides* in the gut microbiome of 3xTg-AD mice prior to the time point at which amyloid-β plaques are modeled. *Bacteroides* have been implicated in health status and are likely key contributors to host-microbial interactions via the gut microbiome-brain axis. Several species of *Bacteroides,* including *B. fragilis*, function ecologically as keystone species, indicated by low relative abundance and disproportionately numerous interactions within the microbial community.[5] *B. fragilis* can influence the gut microbiome-brain axis by producing neurotransmitters (e.g. GABA), modulating serum metabolites, and modulating GI inflammation.[6] In recent studies of AD, *Bacteroides* were increased in relative abundance in mice expressing a variant of human APP (APPswe [Tg2576]) compared to control mice and were positively correlated with amyloid-β burden.[7] We have challenged mice with *B. fragilis* for up to 52 weeks

and leveraged a collaboration with Dr. Carol Barnes to measure different aspects of cognition, vision and emotion that depend on different brain areas. Dr. Jonathan Lifshitz advised our team on neuropathological assessments. This analysis will provide a more complete picture of the role of microbiome manipulation in mice modeling AD pathologies.

The gut microbiome is directly tied to immune development and response throughout the lifespan. Age associated chronic inflammation underpins many aging associated diseases, including neurodegenerative disease.[8] Mounting evidence suggests that gut microbiome alterations and peripheral inflammation are associated with AD, though the mechanisms and relationship to AD pathologies have not been well defined.[9,10] One pathway that contributes to chronic inflammation is through oxidative stress, which is the imbalance between the production of reactive oxygen species (ROS) and the availability of endogenous antioxidants to scavenge ROS.[11] Dr. Traustadòttir has demonstrated that acute exercise leads to increased nuclear erythroid factor 2 (Nrf2) signaling, a master regulator of antioxidant defenses, but that Nrf2 signaling was impaired in older individuals due to chronic redox stress.[12] Exercise can alter the composition of the gut microbiome and can influence chronic inflammation and oxidative stress; a recent study demonstrated that the gut microbiota in aged mice drives age-related oxidative stress and mitochondrial damage in the microglia.[13,14] Additionally, phytonutrients, such as sulforaphane (SFN, derived from cruciferous vegetables), increase Nrf2 signaling *in vitro* and *in vivo*, and may rescue the effect of exercise in aging individuals. SFN restructures the GI microbiome,[15] which may contribute to protection against oxidative stress and protection against development of AD. We are in the process of analyzing the fecal microbiome and markers of intestinal inflammation pre- and post- intervention with SFN and acute exercise. Understanding the trajectory of microbial alterations during healthy aging will allow us to develop a framework for studying the microbiome in AD.

**Preliminary Data:**

With support of the AAC, we have recently published a study that demonstrated unique temporal gut microbiome signatures of AD pathologies in 3xTg-AD mice and genetic controls (WT).[16] Fresh fecal pellets were collected fortnightly for 52 weeks bacterial microbiome analysis. Three statistical approaches used in this study 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.

**Experimental Design and Methods:**

For Specific Aim 1, we compiled publicly accessible human and mouse gut microbiome data, as well as healthy human gut microbiome data and multiomic data (when available) from the NCBI Sequence Read Archive and the Qiita microbiome pooled analysis database and are integrating these datasets for a pooled analysis. These analyses will be performed using QIIME 2, developed in Dr. Caporaso's Lab. We will apply multiple methods for integrating microbiome feature types using existing and planned QIIME 2 plugins. This will include integration of ASVs and metabolites with neural networks using mmvec[17], development of machine learning classifiers with q2-sample-classifier[18], and the application of other tools currently in development.

For Specific Aim 2, 3xTg-AD and WT mice were challenged fortnightly with *Bacteroides fragilis* ($10^{10}$ CFU in 1mL of applesauce) or a vehicle control and were aged to 52 weeks (n=10 mice/group/strain). Neuropathology and inflammatory response. We used reverse transcriptase qPCR to measure inflammatory gene expression in the ileum, colon, and brain (frontal cortex and hippocampus) from mice using an array for Th1/Th17 responses, astrocyte reactivity, microgliosis, and GABA receptors.[19,20] We also used behavioral and cognitive tasks as outcomes. The first was the spatial version of the Morris water maze task, which is a test of spatial memory that depends on the function of the hippocampus, a structure sensitive to AD pathology in

humans.[21] The second task was the temporal ordering task which is used to explore the interaction between the prefrontal cortex and the hippocampus.[22] The next task to examine anxiety levels in the animals using an elevated T maze will be used to tap into circuits including the amygdala.[23]

For Specific Aim 3, Dr. Traustadòttir has an ongoing interventional study in older adults from which we will recruit for gut microbiome analyses. We will recruit up to 25 older (≥60y) men and women in equal numbers. Study participants will be healthy, not overly obese (BMI ≤33.0 $kg/m_2$), non-smokers, and have no contraindications to maximal exercise. This randomized crossover study involves three visits. First, participants will complete a screening visit and undergo testing of aerobic capacity. If they consent to participate, they will be given three fecal collection kits; one to be collected prior to the intervention, one to be collected after the first intervention (SFN or Placebo + Exercise), and one to be collected after the completion of the second intervention (SFN or Placebo + Exercise) after a >7 day washout period. GI microbiome composition and function will be compared to subject activity level, aerobic capacity ($VO_2$ peak test and graded exercise test), Nrf2 and downstream gene expression, and high and low responders using QIIME2.

**Proposed One-Year and Long-Term Outcomes:**

We have recently published a manuscript in Microbiology Spectrum as a direct result of AAC support.[16] In the next year, we anticipate submitting 1-2 additional manuscripts into high-impact journals. We have also identified PAR-22-093 (research on current topics in ADRD) to submit an R01 during this funding year.

**Year End Progress Summary:**

**Progress toward Aim 1:** We are performing a pooled analysis where we are obtaining raw microbiome sequence data and associated metadata from as many of these studies as possible, and analyzing them using consistent and current best practices for microbiome data analysis. This will enable us to validate that findings from prior work are robust to data analysis methods, and to identify patterns that emerge across studies. Sixteen studies have been included at this time. Five of those studies are currently being used for this meta-analysis. We have not yet been able to obtain data for six studies identified by our search terms, we plan to reach out to these investigators individually. The remaining six are shotgun metagenomics and are planned for future analyses. To confirm the microbial trends found in these studies we analyzed each of these studies individually using QIIME 2. This step allowed us to match findings of our analysis with relevant results in each study. This serves as a sanity check for each study and provides the basis for us to identify trends across studies. In Borsom et al. the investigators (our team) observed a significant difference in gut microbiome diversity between 3xTg mice and control (WT) mice at 8 weeks of age using Bray-Curtis dissimilarity ($p < 0.0001$) and we were able to confirm this finding ($p<0.0001$).[16] Bello-Medina et al. stated a significant difference in beta diversity between Not Tg vs. 3xTg-AD females at 3 months old ($p = 0.018$), which we were also able to confirm ($p<0.0001$).[24] Zhang et al. found that the Simpson diversity index (an α-diversity metric) was significantly higher in AD Tg mice compared to WT (unconfirmed).[25] They noted that in a principal component analysis 3xTg-AD mice clustered differently from WT mice, which we confirmed ($p = 0.001$). While we have encountered some challenges in this analysis, these are all typical of microbiome pooled analyses. Our teams are world experts in microbiome data analysis, making us an ideal group to perform this work.

**Progress toward Aim 2:** We have performed gene expression analysis of the frontal cortex of mice treated with *B. fragilis* at baseline (8 weeks), when amyloid plaques are modeled (24 weeks), and when both plaques and tauopathy are present (52 weeks). Key behavioral and cognitive assessments were performed when mice reached the final terminal timepoint, 52 weeks. Analysis

of gene expression demonstrates reduction of tight junction (*cldn1*) gene expression in 3xTg-AD mice treated with *B. fragilis* at 52 weeks compared to wild type mice at 52 weeks, but this was not significant in 3xTg-AD mice treated with the vehicle control. Interestingly, we find that GABA receptor expression is decreased in the frontal cortex 3xTg-AD mice at 52 weeks of age compared to WT mice at 52 weeks, regardless of *B. fragilis* treatment. This may indicate that a reduction in GABA signaling may be characteristic of AD when pathologies are present. Serum and fecal untargeted metabolomics demonstrates significant differences in fecal and peripheral metabolites across our treatment groups, and we are currently quantifying potential bacterial-derived neurotransmitters using targeted metabolomics. We performed the Morris Water Maze (MWM) to assess spatial learning and the Temporal Object Recognition (TOR) test to evaluate prefrontal cortex/hippocampus interaction. We did not observe any significant differences in MWM or TOR across our treatment groups.

**Progress toward Aim 3:** We have obtained IRB approval and have begun selecting participants for the study. Preliminary results suggest that the SFN supplement works well *in vitro* to suppress nrf2 signaling and oxidative stress using PBMCs derived from participants pre- and post-exercise challenge. However, new results suggest that the outcomes are limited *in vivo* when participants are supplemented 90 minutes prior to exercise. This is likely due to a host enzyme cleaving the SFN, so we are moving to a different supplement using whole phytonutrients.

Toward our **long-term outcomes**, support from the Arizona Alzheimer's Consortium has resulted in **acceptance of a manuscript in Gut Microbes (IF 12.4)** that describes the potential role of bacterial-derived neurotransmitters in aging and AD (http://dx.doi.org/10.1080/19490976.2024.2371950). We have an R01 in development to further investigate the role of microbiome-derived GABA in development of AD pathologies.

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# ARIZONA ALZHEIMER'S CONSORTIUM
# 2023-2024 Scientific Progress Report

**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 Cerino, PhD, Megan McCoy, PhD. College of Social and Behavioral Sciences, Northern Arizona University; Arizona Alzheimer's Consortium.

## Specific Aims:

Specific Aim 1: Determine care dyad preferences for (1a) identifying and monitoring cognitive and behavioral symptoms of Mild Cognitive Impairment (MCI) due to AD and for (1b) engaging in remotely-delivered supportive intervention to contend with or reduce symptoms and associated problems from MCI.

Specific Aim 2: Identify essential components of a culturally-appropriate intervention by exploring rural care dyads' 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.

Specific Aim 3: Examine the impact of modifiable protective and risk factors on daily cognitive health among rural individuals with MCI including caregiver factors and dyadic factors, as well as psychosocial, sociocultural, and contextual social determinants.

## 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 untrained 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].

Despite these pressing needs, there are currently few interventions specifically designed for rural care dyads, including early detection of Mild Cognitive Impairment (MCI) and remote delivery of support[9,10]. 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 this research is to develop accessible, culturally-informed, and scalable intervention technologies and resources to identify and support rural care dyads with MCI due to 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[11].

## Preliminary Data:

Previous studies by our interdisciplinary team from social work (McCarthy, McCoy) and psychological sciences (Cerino) are foundational to the Aims of this study. Dr. McCarthy possesses topical expertise in the needs and assets of diverse dementia caregivers in Northern Arizona[8,12], as well as experience with dyadic research, participant engagement, and intervention development[13–17]. Dr. McCoy's expertise in community-based aging research has documented the importance of senior centers as ideally situated and trusted community-based sites with unrealized potential to support rural older adults with MCI due to AD and their caregivers[18–23]. Dr.

Cerino specializes in identifying modifiable daily psychosocial factors related to cognitive aging through mobile technologies and advanced statistical modeling[24,24–26].

**Experimental Design and Methods:**

The goals of this mixed-methods feasibility study are to use a community-based approach to better understand care dyads' access to and preferences for remote MCI monitoring and intervention technology, as well as to identify essential components of a culturally-tailored intervention for rural care dyads coping with MCI. We also seek to determine the impact of modifiable risk and protective factors on daily cognitive health among rural individuals with MCI.

To achieve Specific Aims 1 and 2, we are conducting semi-structured qualitative interviews with up to 30 care dyads living in rural Northern Arizona (or until theme saturation is reached). Interview questions focus on dyad preferences for identifying and monitoring symptoms of MCI, as well as for engaging in remotely-delivered interventions. We are obtaining Likert-scaled ratings of preferred symptom identification/monitoring and intervention technologies, as well as participant demographics and individual, dyadic, and environmental/contextual factors that may impact the dyad's experience with and adjustment to MCI via a baseline survey administered to each member of the dyad. Participating dyads are offered a $100 electronic gift card in appreciation for their time for completing the qualitative interviews and baseline survey. To achieve Aim 3, we are collecting additional daily diary mobile survey data from individuals with MCI (i.e., those who participate in Aims 1 and 2 and then opt in to Aim 3). Fourteen consecutive days of survey data are collected via project smartphone about the individual's daily experiences of stress[27], control[27], social support[28], social company[25], and access to care and transportation. After each survey, participants complete three brief objective cognitive tasks to assess: (1) spatial working memory, (2) processing speed, and: (3) object-feature relational memory binding. In appreciation for their time completing the Aim 3 protocol, participants are offered an additional $50 electronic gift card.

**Proposed One-Year and Long-Term Outcomes:**

Proposed one-year outcomes for this study include: (1) To determine culturally appropriate methods and technologies for identifying rural dyads with MCI in community-based settings; (2) To establish content needed to develop an intervention for this population; (3) To construct a profile of rural caregiver-receiver dyads that includes modifiable risk and protective factors that influence cognitive health in everyday life; (4) To establish collaborative relationships with regional senior centers that will be needed for future research with rural MCI/AD care dyads, and; (5) To educate rural communities to promote memory screening and the importance of early detection. Longer-term outcomes include allowing the Co-PIs to work toward a shared vision of community-based intervention development and to provide preliminary data to inform an R61/R33 National Institute of Health (NIH) Interdisciplinary Aging grant application.

**Year End Progress Summary:**

*Outcomes (1 and 2) Progress*: To date, we have conducted qualitative interviews with 8 rural dyads (8 individuals with MCI, 7 caregivers), with 3 additional participants enrolled . This has resulted in approximately 609 minutes of audio recordings which have been transcribed into 215 pages of raw transcripts and subsequently validated for accuracy. In addition, 23 dyads identified through senior center and other partners in Northern Arizona (e.g., Dignity Health Memory Clinic in Prescott) have expressed interest in being screened for enrolment in the study and 4 dyads are in the process of being screened (i.e., playing "phone tag"). Our research team continues to actively develop and reinforce partnerships, as well as screen participants, as data analysis continues and we assess our progress toward theme saturation at which point we will conclude participant recruitment, screening, and enrollment.

Data analysis for outcomes/aims 1 and 2 is underway. Preliminary themes suggest that there is general interest in using technology to support individuals experiencing MCI, with participants

sharing ideas such as interactive brain activities, monitoring, and memory tracking applications. However, experience and comfort levels with using specific technologies vary, and some participants suggest education or support that includes a live component (either a counselor, or peer engagement) could also be helpful. This is consistent with a scoping review that our team published this year on the topic of the feasibility and utility of mobile health applications in rural communities[29]. Some participants point to generational differences, resistance to technology, lack of interpersonal connection, and complexity of technology as potential disadvantages of using technology to support memory. Challenges among those experiencing MCI and/or cognitive decline relate to fear (particularly in cases where there is a family history of dementia or Alzheimer's) and feelings of shame, frustration, and anxiety around memory loss. In terms of culturally tailored supports in Northern Arizona, participants describe a lack of services related to memory, including trained professionals and caregivers. Participants also share that if there was a cost associated with using technological interventions to support memory this may be a barrier to receiving support in rural communities. This finding is also consistent with our team's scoping review[29].

*Challenges (Outcomes 1 and 2)*: Participant recruitment has been slower than anticipated because of the community-based methods we are committed to employing in order to promote long-term engagement from our senior center partners (see Outcome 4 below). These methods hinge on developing trust with the leadership, staff, and clientele of community-based organizations. This trust-building takes time but we are hopeful that it will result in deep commitment from our partner agencies in the immediate and distant future. Traditional approaches to participant recruitment lean more heavily upon referrals from healthcare providers and various convenience sampling strategies including advertising in print and social media. We have received referrals from the Prescott Memory Clinic and are working to strengthen that partnership. In May 2024, we developed a Facebook page dedicated to the study and are beginning to place recruitment ads in rural newspapers.

*Outcome (3) Progress*: To date, we have enrolled 8 individuals with MCI in Specific Aim 3 (6 completed, 2 still doing the 14 day mobile protocol). Preliminary findings from the 14-day mobile protocol suggest that people with cognitive impairment in rural Northern Arizona are willing and capable (and sometimes enthusiastic) of completing daily mobile cognitive health assessments, demonstrating feasibility and a need for additional data collection in Year 2.

*Challenges (Outcome 3)*: Participant recruitment has been slower than we anticipated because we have been exercising patience in the development of meaningful partnerships with community-based senior centers. We believe we are laying the necessary groundwork for a sustainable and relevant program of research with the diverse rural communities in our region.

*Outcome (4) Progress*: In the past 12 months, we have taken great care to develop close and authentic relationships with senior centers. In order to gauge capacity and interest in partnering, we developed and disseminated a survey to 23 centers in Coconino, Apache, Gila, Mojave, Navajo, and Yavapai counties. With minimal prompting, six center leaders responded representing 380 unduplicated daily center participants from diverse races and ethnicities and speaking languages including English (6 of 6 centers), Spanish (3 of 6 centers), and Diné bizaad, Mojave, Havasupai, or Hopi (2 of 6 centers). All six centers offered activities to support brain health such as "game days," although only two offered workshops related to memory and dementia, screening, and referral services. Three of six centers provided workshops and resources for caregivers and two centers ran caregiver support groups. Six centers reported having free Wi-Fi access for participants and four reported having access to computers on site, although no centers had iPads or other tablets available for on-site use or by loan. Four centers offered educational workshops about technology and three offered on-on-one support.

Only one center reported having participated in a research study in the past, although all six reported being interested in doing so, particularly if there were educational and support benefits for participants, as well as the potential to grow center resources. These data illustrate existing resources for rural MCI dyads in our region but also provide evidence about resource gaps that can inform our efforts to develop supportive technologies. One next step in this effort is to continue to build relationships with these 6 centers by providing on-site Brain Health and other educational workshops (see Outcome 5 below). Another next step is to reengage the centers who did not respond to the capacity survey (i.e., by offering to provide a workshop if they feel it would be beneficial) in order to grow our network of partners.

*Outcome (5) Progress*: As an early step in relationship building (i.e., before directly requesting assistance with participant recruitment), we delivered Brain Health Workshops to centers in Flagstaff, Yarnell, Bullhead City, and Prescott (4 total). We also conducted 9 education, screening, and referral "tabling" events at the Montoya Center in Flagstaff, two tabling events at the Center on Rosser in Prescott, and one presentation and tabling event at the Coconino County library. We disseminated information about the study and about brain health in general at the NARBHA Institute-sponsored *Aging Well Arizona* (November 2023) event in Flagstaff, at the So' Tsoh Foundation and Arizona Department of Health Services-sponsored *Caregiver Summit* (April 2024) in Window Rock which included presentations and roundtable discussions alongside Navajo, Hopi, and Zuni caregivers, and at the *Exploring Goals of Care in Tribal Communities* conference (June 2024). At the regional level, student personnel Goldtooth and Livingston presented a poster on our study's protocol with status report on recruitment at NAU's Research Symposium in April 2024. At the national level, we presented.one paper on psychosocial correlates of cognitive health at the Annual Meeting of the Gerontological Society of America in November 2023 and will present two papers on findings from the current data collection at the Annual Meeting of the Gerontological Society of America in November 2024.

**Progress made toward proposed long-term outcomes:**

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 currently have a manuscript describing our community-based research process with senior centers in development for submission to the Journal of Rural Health. We participated in an NIH-sponsored Team Science workshop in January 2024 and begun conversations with an NIH-NIA Program Officer about fundable Aims for a larger study. An auxiliary project has been to work with local community organizations including the NARBHA Institute and Northern Arizona Alzheimer's & Dementia Alliance (NAZADA) to achieve the designation of a *Dementia Friendly Community*, as well as to organize within NAU to work toward achieving the designation of an *Age-Friendly University*.

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# TRANSLATIONAL GENOMICS RESEARCH INSTITUTE
# PROJECT PROGRESS REPORTS

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Identification of Genetic Variants Associated with Exceptional Verbal Memory Performance in Aging.** Matthew Huentelman, PhD, Ignazio Piras, PhD, Carol Barnes, PhD, Meredith Hay, PhD, Roberta Brinton, PhD, Lee Ryan, PhD. Translational Genomics Research Institute; University of Arizona; Arizona Alzheimer's Consortium.

**Background and Significance:**

Much of the genetic contributors to learning and memory performance are still left to be elucidated. Our MindCrowd study, which has been recruiting since 2013, has amassed a cohort of ~100,000 individuals who have agreed to be re-contacted for additional scientific research. MindCrowd assesses cognition via two tasks – a simple visual reaction time test and a verbal memory task known as paired associates learning (PAL). PAL is a form of episodic memory, a key memory type that is notably influenced by Alzheimer's disease and is typically one of the first memory forms that are affected by the disease process. We have successfully collected and purified DNA from the MindCrowd cohort using self-collected dried blood spots (DBS) and/or cheek swabs – including hundreds of samples from top performers in MindCrowd. In this project we propose to perform whole genome sequencing to assess genome-wide variants that may be linked to exceptional performance on the PAL test by sampling those individuals in the top 5% of performers for their respective age, sex, and educational attainment group.

**Preliminary Data, Experimental Design, and Methods:**

We have already collected DBS from over 200 individuals in the top 5% of performance. We have isolated DNA and analyzed it for the APOE allele – a common polymorphism with known association to Alzheimer's disease. The APOE E4 variant is known to be a risk factor while the E2 allele is a known protective factor at this locus. Interestingly, individuals in the top performing category are enriched for the E2 allele suggesting that this allele may also be associated with enhanced cognitive performance in addition to being protective for AD. During this project we will assess the tens of millions of other genetic changes in this group to examine for other factors that may be associated with exceptional cognitive performance. The most exciting aspect of this search is our ability to identify rare variants with large effect size. This will be our first chance to search for such variants in a population that was pre-screened for memory performance – essentially the approach we propose will allow us to focus on demographic-adjusted outliers in cognitive performance.

We will utilize our already collected, isolated, and purified DNA from the top 5% performers by age, sex, and educational attainment. Additionally, we will continue to request and collect samples from the top 5% in MindCrowd during the grant period. Sequencing will be performed via short-read Illumina technology and will be conducted at ~35X on average. Association will be performed using a case:control design by comparing allele frequencies in the top 5% cohort with known allele frequencies in the general population. This will result in candidate variants associated with PAL performance and to confirm these variants we will assess a random sampling of MindCrowd that will cover the entire PAL scoring spectrum.

**Proposed One-Year and Long-Term Outcomes:**

By the end of the grant period we expect to have our candidate list in hand based on the top performers. These data will be utilized in a Federal NIH grant to pursue validation genotyping and more extensive genotyping of the MindCrowd cohort. This grant will include additional collaborations within the State of Arizona to investigate the putative biological implications of the associations – including organoid, cell culture, and animal behavior experiments.

**Year End Progress Summary:**

We completed the sequencing of 100 top performers identified in the MindCrowd study. The sequencing data was also utilized to perform “joint” variant calling, which combines all of the sample together to determine their genetic variant profiles as one single batch. This approach is necessary to limit the subtle differences that can exist across analysis batches. The called genetic variants were utilized to determine APOE genotype status and AD polygenic risk – both of these demonstrated lower dementia risk profiles than would be expected from a random sample. This suggests that top performer status is, in part, determined by a lower than average risk for AD-related dementia. Currently we are finalizing the genetic variant calling and comparing the resulting data to public databases. The goal of this work is to search for both common and rare variants that may be enriched in the top performer cohort. This work will be completed by the end of July.

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Analysis of Single Nuclei Sequencing in Parkinson's Disease with Dementia, Frontotemporal Dementia, and Alzheimer's Disease Across Multiple Cell Types in the Frontal Cortex.** Kendall Van Keuren-Jensen, PhD, Eric Reiman, MD, Rita Sattler, PhD, Benjamin Readhead, MBBS, Qi Wang, PhD, Diego Mastroeni, PhD, Thomas Beach, MD, Geidy Serrano, PhD. Translational Genomics Research Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium; Barrow Neurological Institute; Arizona State University; Banner Sun Health Research Institute.

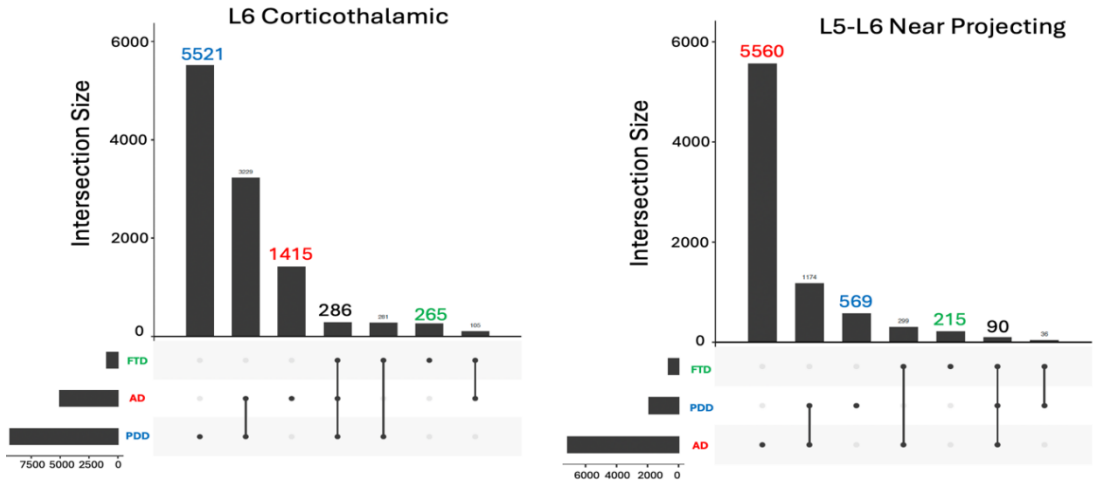
**Specific Aims:**
Examine gene expression differences and similarities between each disease type and their respective controls – for each major cell type identified in the frontal cortex. The goal is to identify deregulated RNAs for each cell type that are common across each dementia (FTD, AD, PDD) and unique to each disease.

**Background and Significance:**
Single nuclei sequencing can reveal cell-level insights into molecular mechanisms of disease.

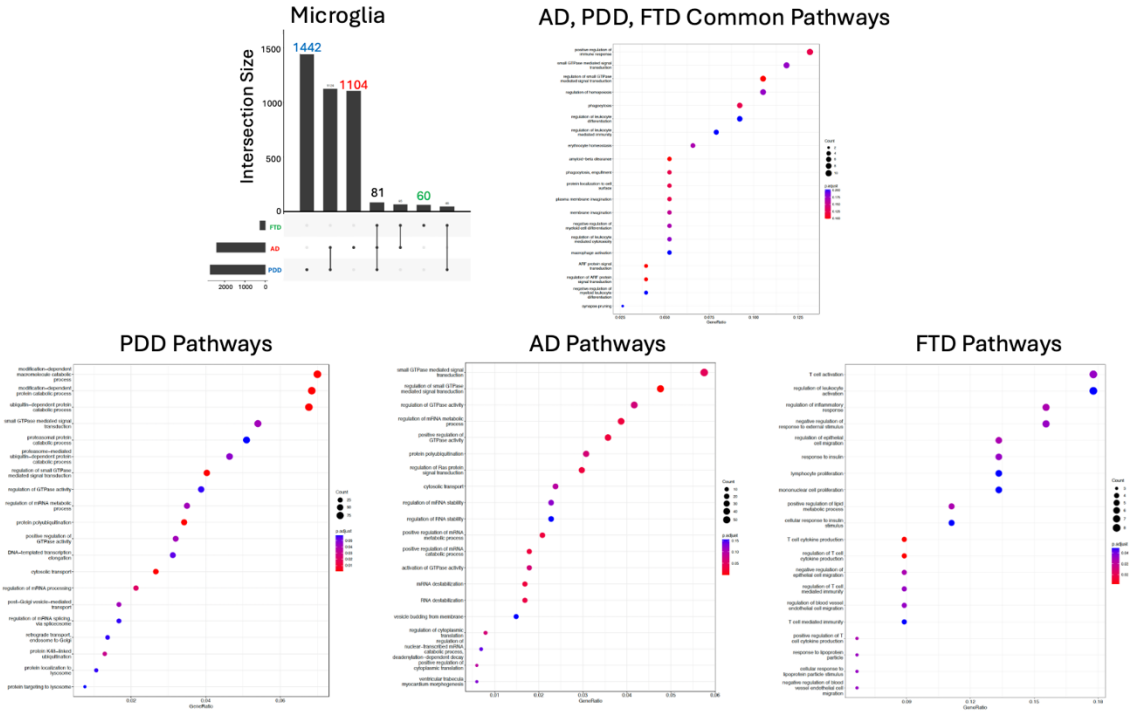
**Preliminary Data, Experimental Design and Methods:**
In collaboration with Rita Sattler, Eric Reiman, Ben Readhead, Qi Wang, Diego Mastroeni, Thomas Beach, and Geidy Serrano, we have generated single nuclei RNASeq data from the frontal cortex of neurologically normal controls (n=47), PDD (n=35), AD (n=35), and FTD (n=15). Because the FTD samples and their controls came from a different site, the PMI for these samples was much longer than the samples received for PDD, AD, and their respective controls. We performed differential expression for each comparison using their equivalent PMI-matched controls. One caveat to note is that the FTD samples have fewer genes detected overall and, therefore, fewer differentially expressed genes.

**Proposed One-Year and Long-Term Outcomes:**
Identify common pathways, per cell type, involved in disease as well as pathways unique to each disease.

**Year End Progress Summary:**
We detected 17 different cell types in the frontal cortex; L2-L3 Intratelencephalic, L3-L5 intratelencephalic Type 1, L3-L5 Intratelencephalic Type 2, L5-L6 Near Projecting, L5 Extratelencepahlic, L6 Intratelencephalic Type 1, L6 Intratelencepahlic Type 2, L6 Corticothalamic, Somatostatin Interneurons, Parvalbumin Interneurons, VIP Interneurons, LAMP5 Interneurons, Astrocytes, Microglia, Oligodendrocytes, OPS, and Endothelial cell types. For each cell type, we performed differential expression for each disease and their appropriate control. We can display the results of our analysis as upset plots. In each upset plot, we display only the differentially expressed genes that are concordant across the diseases. Therefore, the gene set that includes overlapping, differentially expressed genes for AD, PDD, and FTD displays only the differentially expressed genes that were going in the same direction for all three diseases. We were able to identify overlapping genes associated with dementia across all three diseases, as well as unique sets of genes differentially expressed in each cell type. Two examples are in the figure below. L6 corticothalamic cells appear to be more largely affected in PDD, with L5-L6 Near Projecting cells are more affected in AD. Interestingly, despite having lower numbers of




detected genes in FTD, we found specific interneuron types to be more highly affected in FTD than AD or PDD. Having these data allows us to do more analysis and hypothesis generating. Taking microglia as an example, the figure below displays the results of pathway analysis done for each group of differentially expressed genes displayed in the upset plot. We examined what common pathways were dysregulated in microglia, across all diseases, by examining the genes that were significantly different between case and control for each disease and concordant (going in the same direction for all diseases). There are obvious common microglia deregulated pathways among all diseases, such as immune activation, phagocytosis, amyloid clearance, and synapse pruning. When examining the individual disease-related pathways, there is still quite a bit of immune deregulation overlap, but for PDD, changes in ubiquitination come up several times, and for AD RNA stability comes up more frequently.



We are working on putting the data from these combined analyses together into at least two manuscripts. We are currently refining the analysis and looking at additional datasets for validation.

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**A CRISPR Knockout Negative Screen to Identify Genes that Lead to Enhancement of Efficacy of Antibodies Targeting Amyloid Beta (Aβ) in Alzheimer's Disease.** Raffaella Soldi, PhD, Tithi Ghosh Halder, PhD, Sunil Sharma, MD, PhD, FACP, MBA. Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

**Specific Aim:**

The specific aim of this project is the identification of genes that interact with the efficacy of the antibodies targeting amyloid β (Aβ) peptides in Alzheimer's Disease (AD) settings through the analysis of CRISPR knockout negative screen in neuronal cell lines generated from AD patient's skin puncture. By Knocking down one by one genes in cells treated with antibodies against Aβ peptides, we will identify genes that influence the expression of Aβ and PTau in the presence of treatment. This study will allow the identification of genes that enhance the efficacy of the treatment, resulting in a better patient selection in clinical trials as well as development of combination therapy to enhance the current treatment in AD patients.

**Background and Significance:**

Alzheimer's disease (AD) is a debilitating disorder that accounts for almost 70% of the cases of dementia worldwide [1], and it has no effective treatment to date. Amyloid-β (Aβ) depositions and hyperphosphorylated tau proteins are the main pathological hallmarks, along with oxidative stress, N-methyl-d-aspartate (NMDA) receptor-mediated excitotoxicity, and low levels of acetylcholine. Particularly, the accumulation of the Aβ peptides leads to synaptic dysfunction, neurodegeneration, and ultimately AD symptoms [2]. A pharmaceutical intervention that has received great attention in recent years for treating AD is the use of antibodies targeting Aβ peptides in the brain [3]. Recruiting the immune system may prevent Aβ peptides from clumping into plaques or remove Aβ plaques that have formed and help the body clear the Aβ peptides from the brain. Reducing these plaques by means of passive or active vaccination against Aβ peptides has been a long-running endeavor but with disappointing results as the impact on disease progression has been minimal. Recently, a Phase III trial in patients with mild-to-moderate AD has provided ambivalent evidence for the efficacy of this intervention [4] [5]. The data gathered to date could suggest that antibodies do not work, mainly because the studies have not been performed in an optimal fashion. The emerging views are that patients should be treated earlier, ideally in the prodromal or symptom free stage, antibody levels have to be high and the correct epitope must be targeted. More studies and clinical trials to fully explore the potential of vaccines are therefore warranted. In this study we propose the use of a new approach and techniques to identify genes that interfere with the efficacy of the antibodies against Aβ peptides, enhancing the efficacy of the vaccine and can be potentially used to develop new combination therapies for AD patients.

**Proposed One-Year and Long-Term Outcomes:**

The primary screen and secondary studies outlined above are anticipated to lead to the discovery of genes that interfere with the efficacy of the antibodies against Amyloid **β** peptides, and either by promoting resistance or enhancing the efficacy in the first year of study. The knowledge of these genes' effects is anticipated to be beneficial in the treatment and prevention of AD, other dementia and neurodegenerative disorders in general, and can be the basis for future drug

development. Our data also support the validity of the arrayed CRISPR screening to identify new therapeutic strategies in AD, and highlights the potential for drug treatment in combination with antibodies against Amyloid **β** peptides in AD patients.

**Year End Progress Summary:**

In the previous year, we analyzed a CRISPR knockout negative screen in neuronal cell lines derived from Alzheimer's disease (AD) patients to identify genes influencing Aβ and PTau expression. We used a kinase inhibitor CRISPR library from Synthego, targeting over 70 distinct kinases and kinase families. This screening identified kinase inhibitors affecting tau phosphorylation levels and neuron survival, leading to the identification of drugs that could be combined with Aβ antibodies for AD treatment. Our findings shown:

- Knockdown of CDK5 significantly reduced tau phosphorylation. CDK5 is a major tau kinase linked to tau pathology in AD. Its deregulation contributes to neuroinflammation, neuronal fragmentation, and the formation of β amyloid plaques.
- Inhibition of CDK5/p25 has been shown to reduce AD pathological hallmarks and improve cognitive performance in vivo.

We then developed trisubstituted pyrazolo pyrimidine compounds showing high specificity and potency for CDK5 inhibition. Five compounds (TGN-102, TGN-1091, TGN-1099, TGN-1102, and TGN-1104) were tested for their ability to reduce tau phosphorylation in AD models. All compounds significantly reduced Ptau levels, with TGN-1099 also affecting total tau expression, suggesting cytotoxicity. TGN-1062, TGN-1102, and TGN-1104 showed high efficacy in reducing Ptau levels in AD neurons, with limited effects in healthy neurons. Viability assays indicated that the compounds were toxic at micromolar concentrations, but effective at nanomolar doses over extended periods. However, kinase profiling revealed TGN-1062 had high affinity for CDK5 but was not selective, showing higher affinity for CDK7 and CDK2. TGN-1102 and TGN-1104, though less affine, were more selective for CDK5. In the past year, optimization of the initial hit compounds to improve their pharmaceutical properties and activity toward CDK5 proved to be challenging, due to the low CDK5 selectivity of the new compounds. An alternative approach to influence the expression of Aβ and PTau in the presence of treatment is needed.

TREM2, a transmembrane receptor on microglial cells, has a high binding affinity to β-amyloid (Aβ) oligomers. This interaction is diminished by AD-linked mutations in TREM2, impairing Aβ degradation in microglia and mouse brains [6]. TREM2 is crucial for phagocytosis of Aβ, influencing various Aβ-induced microglial responses, including cytokine expression, migration, proliferation, and morphological changes [7]. A possible new approach would be enhancing TREM2 activity to improve phagocytosis of diseased brain cells, clear amyloid plaques, reduce tau pathology, and lower neuroinflammation.

To test this, we developed and characterize novel TREM2 agonists using both cell-free and cell-based methods. Synthetic chemistry approaches were used to create analogs, which were then tested for their effects on key microglia phenotypes in vitro using primary human iPSC-derived microglia and human HMC3 microglia cultures [8]. A literature review suggested that molecules with a benzo/pyrido-pyrimidine core might activate TREM2 [9, 10]. Molecular dynamic simulations showed better binding of these molecules to a key pocket on TREM2 protein[11, 12].

We designed new chemical entities (NCEs) with benzo/pyrido-pyrimidine or benzo/pyrido-diazepine core systems, which revealed to be more stable in TREM2 binding pocket. We used in silico-based multi-parameter optimization (MPO) to improve brain penetration and synthesized seven compounds (TGN-T001 to TGN-T007). Using the in-cell thermal shift assay (CETSA) [13], we confirmed that compounds TGN-T001, TGN-T002, TGN-T005, and TGN-T006 stabilized

TREM2. These compounds also induced SYK phosphorylation, indicating TREM2 activation [14, 15], in human microglia HMC3 cells. Additionally, TGN-T001, TGN-T004, TGN-T005, TGN-T006, and TGN-T007 increased Aβ phagocytosis capacity in HMC3 cells [16]. Pharmacokinetics and brain accumulation studies in mice showed that TGN-T001 had 21.7% oral bioavailability with a good half-life and brain penetration, while TGN-T006 had 90% oral bioavailability but a shorter half-life and lower brain/plasma ratio. Ongoing studies aim to optimize these initial hits to improve their pharmaceutical properties.

- No publications or posters are currently in preparation; further studies are in progress. No new collaborations arose from this project.

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# UNIVERSITY OF ARIZONA
# PROJECT PROGRESS REPORTS

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Behavioral and Neuroimaging Network Biomarkers of Brain Aging and Alzheimer's Disease**. Gene E. Alexander, PhD (PI), David A. Raichlen, PhD, Christian G. Habeck, PhD, Theodore P. Trouard, PhD. University of Arizona; University of Southern California; Columbia University; Arizona Alzheimer's Consortium.

**Specific Aims:**

We will address the following specific aims: 1) to determine how physical activity (PA) and sleep quality (SQ) influence cognitive and brain aging in highly active versus typically active older adults with differential risk for AD; and 2) to further develop, evaluate, and apply novel methods of analysis of brain imaging data to identify robust and reproducible neuroimaging network patterns of age-related cognitive dysfunction and AD risk. Additionally, we expect this proposal will provide important added value by: 1) evaluating novel wearable biomarkers for use in the NIA Arizona ADRC Biomarker Core and other collaborative projects, 2) helping to create the infrastructure, methods, and a unique set of analytic tools to support applications in cognitive aging and AD research for large-scale datasets across Arizona and nationally, 3) exploring how neuroimaging measures of key brain structures, including the hippocampus and frontotemporal white matter relates to PA and SQ in older adults; 4) evaluating how PA, SQ, and their associated neuroimaging networks relate to fluid biomarkers of brain pathology, and 5) supporting new external grant proposals on aging and AD risk by Arizona researchers and collaborators.

**Background and Significance:**

The older adult population is expected expand greatly over the next several decades. It will be critically important to address the corresponding growth in AD within Arizona and nationally. It is widely accepted that APOE ε4 genetic and cerebrovascular health factors can increase the risk for AD. In contrast, engaging in PA can enhance cognitive function in aging and reduce AD risk, yet the specific types of daily activity and associated mechanisms underlying their effects have yet to be fully elucidated. Research with highly active older adults is needed to identify how PA influences healthy brain aging and AD risk. SQ is another critically important aspect of our daily activity that impacts brain aging and AD risk. Differences in sleep, as well as daytime sedentary behavior, can have important impacts on brain aging and AD risk that are distinct from engagement in PA, and there is growing interest in how these different lifestyle behaviors interact to alter the risk for AD. The use of multivariate network analysis methods and machine learning algorithms have garnered increasing interest by providing new approaches for identifying highly sensitive markers of aging and disease risk. How these novel approaches can be best applied to large-scale datasets to identify highly robust and reproducible patterns in neuroimaging, behavioral, and fluid biomarker data has yet to be determined.

**Preliminary Data, Experimental Design and Methods:**

We have previously shown that larger hippocampal volume was related to more moderate to vigorous exercise and greater cardiorespiratory fitness was associated with larger total brain volume (Raichlen et al., *Brain Imaging Behav*, 2020). We also showed that air pollution can attenuate the benefits of PA on brain volumes and the subsequent risk for AD (Furlong et al., *Neurology*, 2022; Raichlen et al., *Med Sci Sports Exercise*, 2022). A review of our prior work on the importance of PA in influencing brain aging and AD risk was published in *Scientific American*, which was featured on the issue cover (Raichlen & Alexander, *Sci Am*, 2020). We have also addressed the importance of human sedentary behavior as a distinct risk factor for brain aging

and AD risk, with an article published in the *Proceedings of the National Academy of Sciences* showing that high levels of cognitively passive daytime sedentary behavior increased the risk for dementia (Raichlen et al., *Proc Natl Acad Sci USA*, 2022).

This project proposed to develop, evaluate, and apply methods to investigate how behavioral and lifestyle measures of PA and SQ relate to brain aging and AD risk by utilizing available large-scale datasets of older adults with ages ranging from 45 to 85+, including from the Arizona ADRC, UK Biobank, and ADNI. Actigraphy and self-report scales of PA and SQ, MRI scans of brain structure, function, and connectivity, cognitive measures, health status and dementia outcomes, and available AD fluid biomarkers were obtained from relevant datasets for development of analytic methods, testing proposed research questions, and replication of findings across cohorts. We planned to leverage support from a complementary NIA R01 grant (MPIs: Alexander, Raichlen, Klimentidis) and the NIA ADRC Biomarker Core (Core Leader: Alexander), to provide access to relevant datasets. We planned to develop, test, and refine new actigraphy and neuroimaging network biomarkers for aging and AD risk. Strengths of this proposal included its focus on: clinical research with important benefits for older adults in Arizona and nationally; "state-of-the-art" PA and SQ methods linked to cognition, neuroimaging, and fluid biomarkers; outcomes that may lead to interventions for AD risk; AAC collaborations for new external grant proposals; creation of unique analytic methods made available to collaborators across Arizona; and development of new technology-based behavioral biomarkers to support our NIA ADRC.

**Proposed One-Year and Long-Term Outcomes:**

This work will be leveraged to support multiple complementary projects investigating effects of PA and SQ on cognition, brain structure, function, and connectivity, and blood markers of AD risk. These studies reflect AAC collaborations focused on developing externally funded grant proposals, as part of a further developing multi-disciplinary, collaborative research program, to identify how differing levels of PA and SQ influence brain aging and AD risk. We believe the proposed research has the potential to provide unique 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 collaborations and proposals for external NIH funding, as well as to further support our ADRC Biomarker Core efforts. Specifically, this project will provide key findings and methods to support planned new grant submissions, including a follow up to a currently funded NIA R56 grant (MPIs: Alexander, Raichlen) and competitive renewal of an NIA R01 grant (MPIs: Alexander, Raichlen, Klimentidis) to further investigate how differences in PA and sedentary behavior influence brain aging and the risk of AD.

**Year End Progress Summary:**

During the past year, we have made excellent progress in our efforts to enhance understanding of how lifestyle factors and physical activity influence brain aging and the risk for AD. We have shown, in a primary research article and subsequent letter published in the *Journal of American Medical Association*, how the risk for dementia related to sedentary behavior rises rapidly in a non-linear manner in older adults that is distinct from engagement in other types of PA, providing important implications for behavioral interventions that may help reduce dementia risk (Raichlen et al., *JAMA*, 2023, 2024). This work garnered significant media attention with a journal press release and was highlighted in over 350 news outlets worldwide. Further, AAC study investigators (Alexander and Raichlen) on this work participated in a comprehensive review article for the field detailing how sedentary behavior can influence brain health over the lifespan (Zou et al., *Trends in Cognitive Sciences*, 2024). We have also demonstrated the novel application of a multimodal network covariance analysis to identify how a blood-based biomarker of cardiovascular risk is

related to subcortical brain structures and white matter lesion load in healthy aging (Song et al., *Neurobiology of Aging*, 2023). Furthermore, we showed how age and APOE ε4 genetic risk was associated with brain white matter lesion load and cognitive function in healthy aging (Van Etten et al., *Journal of the International Neuropsychological Society*, 2024) and how a novel multimodal MRI hippocampal-related network covariance pattern of regional white matter lesion volumes was associated with cognitive and brain aging (Van Etten, et al., *Frontiers in Aging Neuroscience*, 2024).

We have also published an article applying a novel mendelian randomization analytic approach to demonstrate a causal relationship between PA and cognitive function (Cheval et al., *Scientific Reports*, 2023); and we have further used mendelian randomization to show that the blood metabolite glutamine may have a causal role in reducing risk for AD (Ramadan et al., *Journal of Alzheimer's Disease*, 2024). We have shown how engaging in physical exercise was associated with different aspects of cognition in oldest old adults, 85 years of age and older (Ho et al., *Geroscience*, 2024) and further validated the use of a battery of computerized cognitive tests for use in oldest-old adults (Nolin et al., *Journal of the International Neuropsychological Society*, 2023). Additionally, we have shown that physical activity was associated with cognitive function in a novel community-based study of companion dogs living in the community, as part of a collaborative canine study of aging and dementia (Bray et al., *Geroscience*, 2023).

In support of this project, we have published articles in the past year on investigating the use of transcranial direct current stimulation (tDCS) to better understand how this novel intervention can help advance cognitive function in older adults (Hausman et al., *Brain Stimulation*, 2023), how tDCS may facilitate working memory capacity (Aksu et al., *Geroscience*, in press) and reduce depression and anxiety in older adults (Hausman et al., *Brain Stimulation*, 2024), how differences in learning performance can influence gains during cognitive training in healthy aging (Hardcastle et al., *Geroscience*, 2024), how a novel visual task activates brain function in older adults (Kraft et al., *Geroscience*, 2023), how differences in memory function relate to functional brain connectivity in healthy aging (Waner et al., *Geroscience*, 2023), and how tDCS can influence a cognitive training intervention for task-based functional connectivity in healthy older adults (Kraft et al., *Geroscience*, 2024). We have also shown how a measure of brain energy metabolism and mitochondrial function measured with MR spectroscopy differs among fronto-temporal brain regions in healthy older adults at risk for AD (Lopez et al., *Geroscience*, 2024) and how cognitive aging impacts differences in the use of random and directed exploration (Mizell, et al., *Psychology and Aging*, 2024).

Importantly, the findings from this AAC project have provided key pilot data and results to support the planned submission of a new NIA R01 application (MPIs: Alexander, Raichlen) to further investigate how differences in vascular function influences brain health during aging and how associated lifestyle/behavioral factors related to the engagement of PA impact the risk for dementia. The work from this AAC project also continues to support plans for the renewal of our currently funded $3.1M NIA grant award (MPIs: Alexander, Raichlen, Klimentidis) investigating how engagement in different types of sedentary behavior can alter the course of brain aging and the risk for Alzheimer's dementia.

This AAC project has also directly advanced methodological developments for our wearable/digital biomarker efforts in support of the $5M Biomarker Core (Core-Leader: Alexander; Core Co-Leaders: Atri, Su), as part of our ongoing $15.7M NIA Arizona Alzheimer's Disease Research Center grant (ADRC PI: Reiman). This Biomarker Core provides access, methodological support, expertise, analyses, and data to Arizona-wide investigators and collaborators nationally for neuroimaging, fluid, and behavioral/wearable biomarkers to support

research in AD and brain aging. Work from this AAC project continues to provide new methods which complement and support ongoing studies of PA and SQ in healthy oldest old adults funded by the McKnight Brain Research Foundation (MPIs: Alexander, Cohen, Visscher, Rundek) to evaluate how lifestyle factors influence cognition and brain aging in adults, ages 85+ years. This complementary effort reflects ongoing collaborations between teams of investigators at the University of Arizona, University of Florida, University of Alabama, and the University of Miami. Initial findings from this work, has identified functional connectivity brain networks associated with cognitive function in this unique cognitively unimpaired oldest-old cohort (Nolin et al., submitted).

# ARIZONA ALZHEIMER'S CONSORTIUM
# 2023-2024 Scientific Progress Report

**Fast Parametric Imaging of the Hippocampus Sub-fields.** Maria Altbach, PhD, Ali Bilgin, PhD, Ted Trouard, PhD, Raza Mushtaq, MD, Craig Weinkauf, MD, PhD. University of Arizona; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

## Specific Aims:

Aim 1: Implement T2 and T1 mapping methods with a DL super-resolution approach to obtain quantitative maps with higher spatial resolution (0.47x0.47x1mm) or same resolution as the 2D pulse sequences (0.47x0.47x2mm) but shorter scan times. In this aim, we will evaluate the performance of the 3D T2 and T1 mapping sequences against the 2D sequences, based on signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) of the hippocampus (HC) sub-fields in anatomical images as well as reproducibility of T1 and T2 maps.

Aim 2: Utilize the best T1 and T2 mapping techniques from Aim 1 to determine T2 and T1 relaxation times from the HC sub-fields in subjects with carotid artery disease (>50% stenosis) and mild cognitive impairment (MCI) and age-matched controls (no carotid artery stenosis and no MCI).

## Background and Significance:

The HC is identified as crucial for declarative memory and is an early site for pathologic changes related to Alzheimer's disease (AD). Volume loss of the HC, as measured from T1-weighted volumetric MRI, is detected in early AD and early stages of dementia. The HC is divided into sub-fields which have different cellular and molecular characteristics and, thus, are thought to be affected differently in pathologic processes related to AD and aging.

There has been progress made in the past two decades in assessing hippocampal sub-fields based on MRI. State-of-the-art technology based on 7T scanners allow high spatial resolution and high contrast-to-noise ratio enabling 3D visualization of the inner hippocampal structures. Limitations of current technology are long acquisition times (~10 min) and limited availability of 7T scanners. Furthermore, data obtained with conventional pulse sequences only allow for anatomical evaluations (e.g., volume changes).

To overcome these limitations, our team at the University of Arizona has developed quantitative T2 and T1 mapping techniques (RADTSE and IR-RADGRE) based on radial MRI methods. The major advantage of the technology is that high-resolution quantitative parameter maps can be generated from a small fraction of the data compared to conventional methods (~4% of data required by conventional methods), thus, significantly reducing the scan time for quantitative imaging.

## Preliminary Data:

As part of the 2022-2023 AAC project we successfully implemented RADTSE and IR-RADGRE for high resolution mapping of the HC at 3T. Improvements on both pulse sequence and reconstruction algorithms resulted in T2 and T1 mapping methods of the HC with high spatial (0.47x0.47x2mm) and temporal resolution (12 TEs for T2 mapping and 40 TIs for T1 mapping) in 6-7 min per mapping technique. In this year's (2023-2024) AAC project, the goal was to improve imaging and reduce scan time to ~ 3 min per mapping technique.

**Experimental Design and Methods:**

**Aim 1:**

Pulse sequence implementation and testing: Implement 3D versions of the pulse sequences for T2 and T1 mapping and adapt them for optimal SNR and CNR of the HC. Test the new methods in a phantom (with T2/T1 values found in the gray and white matter of the HC) and compare to 2D methods. Select the best method and parameters to test in vivo, evaluate reproducibility.

Improving spatial resolution via deep-learning (DL). Apply a super-resolution DL approach, developed by our team, to synthesize <1-mm slice thick data acquired in a shorter scan but with lower through plane resolution. Compare image quality and T2/T1 reproducibility against the longer scan acquired with higher through plane resolution.

In vivo evaluation. The HC sub-fields will be delineated by an experienced neuroradiologist (Dr. Mushtaq) using an established atlas. Sub-field image quality will be assessed from T2- and T1-weighted images generated from RADTSE-RADGRE. T1 and T2 reproducibility will be evaluated from the repeated scans.

**Aim 2:** Use the best T1 and T2 mapping technique from Aim 1 to acquire data on 10 subjects with carotid artery disease (>50% stenosis) who have MCI and 10 age-matched controls (no carotid disease and no MCI). Subjects are recruited from a cohort enrolled in Dr. Weinkauf's ongoing R01-AG070987-02. Sub-fields will be identified by Dr. Mushtaq as described above. Evaluate volumes as well as T1 and T2 values in the two groups of subjects to assess differences between the groups. We expect to find greater differences based on T1 and/or T2 mapping (or a combination of both) compared to volumes.

**Proposed One-Year and Long-Term Outcomes:**

1-year outcomes: Results obtained will be used as preliminary data in extramural funding applications for the development of novel brain imaging technologies for high resolution imaging of the HC (e.g., NIBIB Brain Imaging Initiative; NIA R01 application focused on ADRD). Our proposal will include novel quantitative imaging of the HC based on T1 and T2 mapping, DWI, DTI, myelin water-fraction mapping, and microvascular imaging (via ferumoxytol). Results will also be included in a multicenter NIH application to study the vascular impact on ADRD. Long-term: Our long-term goal is to investigate the use of the proposed quantitative imaging techniques to monitor molecular/cellular changes in the HC sub-fields in vascular related dementias and other applications for which we will seek to extend our collaboration to the larger neuroimaging community in Arizona.

**Year End Progress Summary:**

**Progress in Aim 1**

Pulse sequence and super-resolution results. We completed the implementation of the pulse sequences for high resolution T1/T2 mapping of the hippocampus and collected data with 2mm and 4mm slice thickness on a total of 22 healthy subjects (12 female, 10 male, age range; 20-82 y/o, mean age: 50.8 y/o). Nine subjects were imaged twice to assess reproducibility.

Data acquired with 4-mm through plane resolution was used in combination with a super resolution (XRES) deep learning (DL) network developed by our team. The XRES-DL network was trained to produce brain images with a through-plane resolution comparable to the in-plane resolution (~0.48 mm). By acquiring data with 4-mm through plane resolution we were able to reduce the scan time required to cover the HC from 6-7 min to ~3 min per mapping sequence. The images acquired with 4-mm through plane resolution have higher signal-to-noise ratio

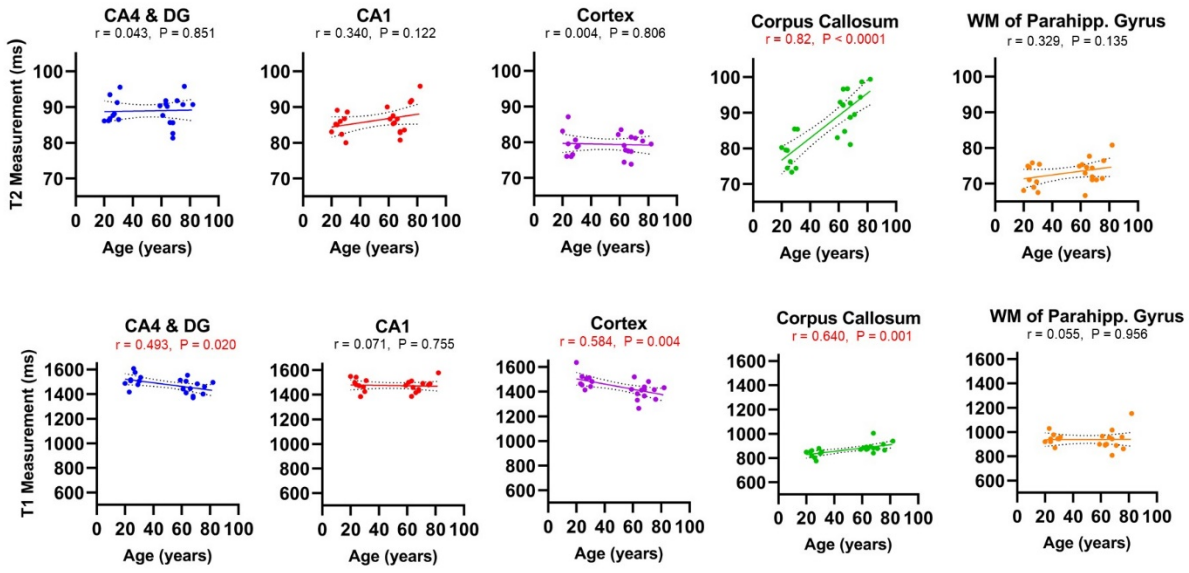
compared to the data acquired with 2-mm through plane resolution improving the overall image quality.

Reproducibility study: We compared the reproducibility of T2/T1 mapping on 9 healthy volunteers that were imaged on two different sessions. Reproducibility was evaluated on the following HC regions-of-interest (ROI): the cornu ammonis 4 (CA4) + dentate gyrus (DG), cornu ammonis 1 (CA1). We also evaluated ROIs in the corpus callosum, cortical grey matter, and white matter of the parahippocampal gyrus.

The linear correlation between the two measurements had a r=0.80 (p<0.0001) for T2 mapping and r=0.96 (p<0.0001) for T1 mapping. Although both T2 and T1 mapping measurements are strongly correlated the r-value for T2 mapping is lower than for T1-mapping. A closer data analysis revealed that our current reconstruction implementation of RADTSE is producing maps where grey matter T2 values are not correct. This was not the case with our initial RADTSE implementation. Thus, we are currently investigating the potential sources or error. Once we correct the problem, we expect the r-value for T2 mapping to align with the results for T1 mapping.

T2 and T1 mapping changes with age: Since the age of our healthy volunteers ranged from 20-82 y/o we evaluated the relationship between T2 and T1 mapping with age. We observe positive relationships in T2 and T1 values with age in white matter and negative relationship in grey matter (see **Fig. 1**). These results are consistent with results found in the literature.

**Figure 1**: Relationship of T2 and T1 values with age.




## Progress in Aim 2

In collaboration with Dr. Weinkauf's group so far, we completed T2 and T1 mapping scans on 5 subjects with carotid disease and MCI (2 female, age range: 65-84, mean age: 76.2, mean MoCA score: 19.6) as well as 7 controls (4 female, age range: 63-76, mean age: 68.4, mean MoCA score: 26.7). We plan to complete imaging and data analysis comparing the carotid disease to the to the age-matched control by the end of the grant period.

# ARIZONA ALZHEIMER'S CONSORTIUM
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**Alzheimer's Disease Research Center (ADRC) Internal Scientific Advisory Committee (ISAC)**. Carol A. Barnes, PhD, Winnie S. Liang, PhD. University of Arizona; Arizona Alzheimer's Consortium; Banner Alzheimer's Institute.

## Specific Aims:

1. To provide administrative ISAC support to Dr. Carol A. Barnes, the chair of the ISAC.
2. To perform grant application management for the ADRC's Developmental and Pilot Grant programs.

## Background and Significance:

Not applicable.

## Preliminary Data, Experimental Design and Methods:

Our ADRC has implemented an effective program for the solicitation, competitive review, and monitoring of an NIA-sponsored two-year ($60K/year) Developmental project, a state-sponsored two-year Developmental project and several one-year state-sponsored Pilot Project grants each year. Dr. Carol A. Barnes directed the distribution of Requests for Funding Proposals, management and identification of external reviewers, organization and collation of reviews. Coordination of activities to support these grant programs were performed by Dr. Winnie Liang, under the direction of Dr. Carol A. Barnes. Dr. Liang also coordinated the distribution of receipt of all applications, organization and collation of reviews, supported ISAC review of applications, communication of funding decisions, and management of the distribution of reviewer honorariums.

## 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:

This year, our ADRC received 15 Developmental Grant applications from five institutions, including ASU, BAI, Mayo Clinic AZ, Midwestern, TGen and UA. Development Grant reviews were performed by 29 external reviewers. The ISAC Developmental Project review meeting occurred on February 5, 2024, with NIA-sponsored Developmental project funding being recommended to Dr. Aneta Kielar (UA). For the state-sponsored Developmental projects, funding was recommended to two researchers, including Dr. Ignazio Piras (TGen) and Dr. Ann Revill (Midwestern).

The ADRC received 20 Pilot Grant applications this year from the following eight institutions: ASU, BAI, BNI, Grand Canyon University, Mayo Clinic AZ, Midwestern, TGen and UA. The Pilot Grant proposals were reviewed by 30 external reviewers. The Pilot Project review meeting occurred on April 22, 2024. For the Pilot Grant program, funding was recommended for three investigators, including Dr. Craig Weinkauf (UA), Dr. Jessica Verpeut (ASU) and Dr. Li Zheng (UA).

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Assessment of the Relation Between Microbiome Composition, Dietary Habits, and Cognitive Status in a Cognitively Well-Characterized Cohort of Older Adults.** Carol A. Barnes, PhD, Emily Cope, PhD, Greg Caporaso, PhD, Elizabeth Glisky, PhD, Lee Ryan, PhD. University of Arizona; Northern Arizona University; Arizona Alzheimer's Consortium.

**Specific Aims:**
Because our interests are in normative aging and variation in cognitive abilities within and across age groups, the focus here is on whether the composition of microbial populations in the gut are related in some systematic way to cognitive phenotypes across the lifespan.

**Background and Significance:**
While there are many reviews and commentaries in the literature suggesting that directly manipulating the bacteria present in the gut may result in cognitive change (e.g., Caracciolo et al., 2014, 2015; Sakar et al., 2016), few have conducted rigorous experiments to examine microbiota in relation to cognition or aging. In fact, one evaluation of the extant data suggests very little support for efficacy of probiotic interventions and positive cognitive outcomes (Romijn and Rucklidge, 2015). While many rigorous experiments have been conducted to examine the interplay between the microbiome and disease states (e.g., Collins et al., 2012; Hsiao et al., 2013; Desbonnet et al., 2015; Keshavarzian et al., 2015; Bajaj et al., 2016; Buffington et al., 2016; Fujimura et al., 2016; Lynch and Pedersen 2016), fewer have focused on 'normal populations'.

**Preliminary Data, Experimental Design and Methods:**
We have a carefully cognitively characterized, and longitudinally studied cohort of individuals that were originally recruited by Glisky, who have been identified as having distinct cognitive profiles. Some of these individuals have very high function in cognitive tasks that rely on the proper function of the frontal lobes, while other individuals show performance scores that suggest that frontal lobe function is low. Other individuals showed performance levels that were very high for their age on tests that examine the function of the hippocampus, while others showed very low performance on tasks that rely on the hippocampus. While many combinations of cognitive performance were observed in the Glisky population, we have identified 10 individuals who were High Performing on frontal lobe tasks and High Performing on Temporal lobe tasks, and 10 individuals that were Low Performing on both frontal and temporal lobe tasks. Members of the Barnes laboratory obtained fecal samples from these individuals, as well as an extensive dietary questionnaire. This will enable us to ask whether there are any bacterial "signatures" that are associated with successful versus non-successful cognitive aging.

**Proposed One-Year and Long-Term Outcomes:**
The data analysis is scheduled to be completed this summer. Dr. Emily Cope will spend a sabbatical year (August 2024-May 2025) with the Barnes lab in Tucson we anticipate making good progress on manuscripts that can come from this collaboration across ADC investigators, and well as our international colleague who is an Affiliate Member of the Evelyn F. McKnight Institute.

**Year End Progress Summary:**
We sent our human and rat samples to Emily Cope to extract the DNA. Once she finished the extraction, she sent the DNA results to Great Caporaso. Greg is analyzing the data presently.

# ARIZONA ALZHEIMER'S CONSORTIUM
# 2023-2024 Scientific Progress Report

**Investigating Gut Microbiome in Individuals with Mild Cognitive Impairment.** Ying-hui Chou, ScD, Daniel Laubitz, PhD. University of Arizona; Arizona Alzheimer's Consortium.

## Project Description:

1) Specific Aim 1: Investigate the differences in the composition of the gut microbiome between individuals with mild cognitive impairment (MCI) and cognitively normal (CN) adults.
2) Specific Aim 2: Assess relationships between the composition of the gut microbiome and plasma biomarkers of beta amyloid and tau.

## Background and Significance:

The human body houses a complex network of microorganisms, with most dwelling in the distal gut. These microbes provide important services to human health, from extracting energy to producing vitamins and warding off pathogens[1]. Colonization of the gut commences at birth and matures by age three, after which the microbiome composition is generally stable[2,3]. Changes to this intricate system have been linked to gastrointestinal and metabolic issues such as inflammatory bowel disease, obesity, diabetes, and insulin resistance[4], as well as neurological conditions such as Alzheimer's disease (AD).

Emerging evidence from animal models and clinical studies point to a possible connection between an imbalance in gut microbes and the development of AD via the gut-brain axis[5,6]. Possible explanations for this link include a disturbed immune system, inflammation of the brain, accumulation of Aβ and tau proteins, a weakened blood-brain barrier, and direct impacts on synaptic plasticity and neural functioning. There is also evidence that AD may have its own unique microbial profile[5].

Determining the relationship between gut microbiome and AD pathology may offer a potential opportunity to modify risk of developing AD. However, to date there have been no comprehensive surveys of whole gut microbiota in humans with preclinical or prodromal AD. In this study, we will perform bacterial 16S ribosomal RNA (rRNA) gene sequencing of DNA isolated from fecal samples to characterize the gut microbial communities in individuals with and without MCI. In addition, we will examine the relationships between the gut microbiota and AD pathology as measured by plasma Aβ and tau.

## Preliminary Data, Experimental Design and Methods:

**Aim 1: Investigate the differences in the composition of the gut microbiome between individuals with MCI and CN adults**

Participants. A total of 30 right-handed participants (50-80 years old), including 15 individuals with MCI (MCI group) and 15 CN adults (CN group) will be enrolled in this study. The following revised Mayo Clinic criteria for MCI[19] will be used for the inclusion of MCI: (a) self- or informant-reported cognitive complaint; (b) objective cognitive impairment; (c) preserved independence in functional abilities; and (d) absence of dementia. The MCI diagnosis will be supported by the measures of general cognitive function using (1) Mini-Mental State Exam (MMSE) 24-27 (inclusive); (2) Montreal Cognitive Assessment (MoCA) 18-26 (inclusive); and (3) Clinical Dementia Rating Scale score of 0.5. The Jak/Bondi actuarial neuropsychological test method[20] and NACC UDS 3.0 Neuropsychological battery[21] will be used to identify MCI (i.e., 1 SD below the age-, sex-, and

education-corrected normative mean on two measures within a cognitive domain, or on three measures across all domains[20]). Cognitively normal adults will be included in the CN group.

Fecal sample collection. Participants will return their fecal samples using overnight delivery sample collection kits, which are packaged in insulated containers and chilled with frozen gel packs. Upon receipt, the chilled samples will be subdivided into sterile bead beating tubes and stored at -80°C until further processing.

16S rRNA amplicon sequencing and processing. The hypervariable V4 region of the 16S rRNA gene will be amplified from each sample using unique for each sample barcoded reverse primers (806R) and forward primer (515F) and with repliQa HiFi ToughMix polymerase (Quantabio). Both reverse and forward primes were extended with the sequencing primer pads, linkers, and Illumina adapters[22]. The PCR will be performed on a the X50 thermocycler (Eppendorf) in the final volume of 40μL. Amplicons will be quantified using Quant-It PicoGreen dsDNA Assay kit (ThermoFisher Scientific, Cat No. P7589), according to the manufacturer's protocol. Equal amount of amplified DNA from each sample will be pooled and the mix of libraries cleaned using UltraClean PCR Clean-Up Kit (QIAquick PCR Purification Kit, Qiagen, Cat No. 28104). Pooled amplicons will be diluted to 4nM and denatured with 0.2N NaOH. The library will be sequenced at the PANDA Core for Genomics and Microbiome Research at the University of Arizona, Steele Children's Research Centre on MiSeq platform (Illumina) with custom sequencing primers[22]. Due to the limited sequence diversity among 16S rRNA amplicons, 10% of the PhiX Sequencing Control V3 (Illumina, Cat No. FC-110-3001) made from phiX174, will be used to spike the library and increase the diversity. The raw sequencing data will be demultiplexed using the *idemp* script (https://github.com/yhwu/idemp). Filtering, dereplication, chimera identification, and merging of paired-end reads will be performed with dada2[23]. The Amplicon Sequence Variants (ASVs) taxonomy will be assigned using the Ribosomal Database Project (RDP) classifier[24] against the most current database.

**Aim 2: Assess relationships between the composition of the gut microbiome and plasma biomarkers of beta amyloid and tau**

Blood sample collection. Blood samples will be collected according to the $C_2N$ Diagnostics' procedural manual[28,29] at the Clinical and Translational Sciences Research Center of the University of Arizona. Venous blood will be collected into one 10 mL $K_2$ EDTA Vacutainer until the Vacutainer is completely full of blood. The blood sample will be centrifuged at room temperature within 30-60 minutes of phlebotomy to separate plasma from cells. Plasma will be aliquoted (0.5-1mL) into Sarstedt micro tubes and frozen immediately on dry ice or in a -80°C freezer within 2 hours of phlebotomy. All plasma sample tubes will be deidentified and stored frozen at the Health Science Biorepository of University of Arizona. Once batched samples are collected, they will be shipped with dry ice by express courier service (Priority Overnight) to the C2N Diagnostics for data analysis.

Plasma Aβ and tau. Plasma samples will be analyzed by the C2N Diagnostics in a blinded manner. The specimens will undergo immune precipitation followed by liquid chromatography-tandem mass spectrometry for quantification of $A\beta_{42}$ and $A\beta_{40}$ peptide isoform concentrations, estimation of $pTau_{181}$ and $pTau_{217}$, as well as identification of ApoE peptides corresponding to ApoE2, ApoE3, and ApoE4 isoforms[28,30]. The following parameters derived from the fluid biomarker analyses will be included in further statistical analyses – $A\beta_{42}/A\beta_{40}$, $pTau_{217}$, ApoE proteotype, and amyloid probability score. The amyloid probability score will be calculated using

a statistical algorithm that combines $A\beta_{42}/A\beta_{40}$ ratio, ApoE genotype (determined by ApoE peptide isoforms) and participant age[28,30]. The plasma biomarkers data will be correlated with the composition measures of the gut microbiome, and multiple comparisons will be corrected.

**Proposed One-Year and Long-Term Outcomes:**

This proposed pilot project aims to enroll 15 participants with MCI and 15 CN adults this year, with an additional 30 participants to be enrolled in the following year. The data collected will be used to apply for an R01 grant in March 2025, the goal of which is to conduct a longitudinal study investigating the relationship between gut microbiome and the progression of MCI. If successful, this project could offer valuable insight into the connection between gut microbiome and cognitive function, leading to improved diagnosis, treatment, and management of MCI.

**Year End Progress Summary:**

Since July 1, 2023, we have successfully gathered AD plasma biomarker data from 36 participants, along with oral microbiome data from 14 participants and gut microbiome data from 9 participants. Blood collection followed the standard operating procedures at the UA Clinical and Translational Sciences Research Center, using a 10 mL K2 EDTA Vacutainer to its full capacity. Post-phlebotomy, the samples underwent centrifugation at room temperature within 30-60 minutes to procure plasma, which was then aliquoted (0.5-1mL) into Sarstedt micro tubes and swiftly frozen on dry ice or stored at -80°C within two hours. The plasma samples, now anonymized, are preserved at the UA Health Science Biorepository. We plan to dispatch these batched plasma samples, safeguarded with dry ice, via express courier to Dr. Nick Ashton at Banner for thorough data analysis.

We have arranged to send the consolidated oral and gut microbiome data to Dr. Daniel Laubitz at the University of Arizona's Microbiome Cores for comprehensive analysis. Each sample's hypervariable V4 region of the 16S rRNA gene will be PCR-amplified using uniquely barcoded 806R reverse primers and 515F forward primers, leveraging repliQa HiFi ToughMix polymerase. We will compute taxonomic richness and evenness using Shannon and Simpson indices. Statistical analyses within each experiment will employ the Kruskal-Wallis rank sum test followed by subsequent Dunn’s multiple comparison test with Bonferroni correction, utilizing the 'dunn.test' R package. Moreover, the comparison of microbial communities between MCI and CN groups will undergo non-metric multidimensional scaling (NMDS) based on Bray-Curtis distances, combined with PERMANOVA to delve into how different metadata variables influence community composition. Additionally, the 'vegan' R package will enable redundancy analysis to explore and visually interpret the influence of metadata variables on species distribution patterns.

We anticipate completing the data analysis for the plasma and microbiome datasets by the end of 2024. Subsequently, our intention is to submit an NIH R21 or R01 proposal early in 2025, focusing on the longitudinal dynamics of the microbiome and its correlation with AD plasma biomarkers in preclinical and prodromal stages of Alzheimer's Disease. The pilot funding we received from the ACC has been instrumental in fostering partnerships with Dr. Nick Ashton and Dr. Daniel Laubitz, paving the way for ongoing collaboration and future grant applications. We extend our sincere appreciation for this support.

# ARIZONA ALZHEIMER'S CONSORTIUM
# 2023-2024 Scientific Progress Report

**Assessment of Associations Between TMS-Induced Plasticity Measures and ATN Biomarkers.** Ying-hui Chou, ScD, Nicholas Ashton, PhD, Breno Diniz, MD, PhD. University of Arizona; Banner Sun Health Research Institute; Banner Alzheimer's Institute; University of Connecticut Health Center; Arizona Alzheimer's Consortium.

## Specific Aims:

**Specific Aim 1: Investigate precuneus synaptic plasticity as measured with iTBS-evoked responses in individuals with MCI and cognitively normal adults**

Study: In this study, 20 individuals with MCI and 20 age-matched CN adults will participate in 3-day assessment sessions. We will evaluate cognitive performance on Visit 1, assess iTBS-evoked fMRI responses on Visit 2, and measure iTBS-evoked EEG responses on Visit 3.

Hypothesis: We hypothesize that individuals with MCI will exhibit diminished responses to iTBS (i.e., lower precuneus plasticity) compared to age-matched CN adults.

**Specific Aim 2: Determine the relationships between precuneus plasticity and ATN biomarkers**

Study: In this study, precuneus plasticity data derived from iTBS-evoked responses in fMRI and EEG will be correlated with the plasma beta amyloid (A), plasma tau (T), neurodegeneration of precuneus and hippocampus (N), and cognitive performance across MCI and CN groups.

Hypothesis: We expect that individuals with lower precuneus synaptic plasticity will exhibit 1) lower level of plasma $A\beta_{42}/A\beta_{40}$ and higher level of tau, 2) lower volume of precuneus and hippocampus, and 3) lower level of cognitive functions.

## Background and Significance:

The precuneus is one of the most connected hubs in the cortex and plays a central role within the default mode network[1-4]. Precuneus is involved in many complex and fundamental processes (such as episodic memory, integration of information, and self-referential mental representations)[5] and is one of the brain regions where the accumulation of Aβ and tau neurofibrillary tangles starts[6-8]. Moreover, atrophy or cortical thinning[9,10], decreased perfusion[11], and lower metabolic activity[12] in the precuneus have been reported in the prodromal stages of AD. It has been suggested that alterations of synaptic plasticity are related to Aβ and tau pathology in hubs such as the precuneus during the preclinical and prodromal stages of AD[8,13]. Dysregulation of synaptic plasticity is probably one of the earliest changes in AD pathogenesis[14,15]. Evidence from rodent models of AD has implicated that impaired synaptic function may occur before the buildup of Aβ plaques and neuronal cell death[16,17], and this degradation of synaptic plasticity could be further deteriorated by Aβ and tau proteins[18].

To date, our understanding of dysregulation of synaptic plasticity in brain regions such as the precuneus is very limited. The questions of how precuneus synaptic plasticity differs between individuals with MCI and CN adults, and how the alteration of precuneus synaptic plasticity is related to Aβ (A), tau (T), and neurodegeneration (N) biomarkers have yet to be addressed in humans at earlier stages of AD. Although the 11C-UCB-J[19-21] or 18F-UCB-H[22,23] positron emission tomography (PET) targeting the synaptic vesicle proteins 2A (SV2A) has recently been developed that allows measurement of synaptic integrity in living individuals, the SV2A PET has not been commonly used for patients with MCI or AD due to the cost of PET scans and the requirement of

on-site cyclotron production of the 11C and 18F tracers. Thus, there remains an urgent need to develop useful, more affordable, in vivo neurophysiological measures of synaptic plasticity.

Transcranial magnetic stimulation (TMS) is a non-invasive neuromodulation technique that has been used in research and approved by the FDA to treat several brain disorders (e.g., depression, migraine, obsessive-compulsive disorders, and smoking addiction). The TMS coil emits a pulsed magnetic field that induces electrical currents in the stimulated brain region, allowing researchers to evaluate real-time modifications of neurotransmission pathways evoked by TMS[24,25]. The action potentials initiated directly by the TMS pulses propagate to cause synaptic transmission at downstream connections via the intracortical axon collaterals[26]. Recordings from rodent studies and from the descending corticospinal tract in humans have shown that TMS can be used to probe synaptic activity in the stimulated brain region[27,28].

Our laboratory has conducted a series of TMS studies investigating LTP-like motor synaptic plasticity in individuals with MCI/AD and cognitively normal (CN) adults[29-31]. Findings of our studies have revealed that individuals with MCI exhibit diminished homeostatic meta-plasticity in the primary motor cortex compared to the CN adults[31]. We also reported that motor synaptic plasticity evoked by iTBS was associated with baseline and iTBS-evoked changes in resting-state fMRI functional connectivity within the sensorimotor areas[32]. Our recently published meta-analysis, consisting of 61 TMS studies with a total of 2,728 participants (1,454 patients with AD, 163 patients with MCI, and 1,111 CN adults), has shown that patients with AD and MCI exhibit impaired motor synaptic plasticity compared to CN adults when repetitive TMS is applied over the primary motor cortex[29]. Here, we will extend our findings from motor synaptic plasticity and leverage our experience with TMS and brain imaging techniques to 1) characterize precuneus synaptic plasticity with imaging derived measures of iTBS-induced neural reorganization and 2) investigate its relationship with the ATN biomarkers in individuals with MCI and CN adults. We expect that findings of our proposed project in conjunction with other biomarkers will enhance our understanding of synaptic plasticity in preclinical and prodromal AD. Additionally, the iTBS-evoked precuneus plasticity may have great potential serving as an outcome measure for clinical trials of intervention.

**Preliminary Data, Experimental Design and Methods:**

Twenty individuals with MCI and 20 age-matched CN adults will be enrolled to 3-day assessment sessions. The primary outcome measures will include functional neuroimaging derived measures of iTBS-evoked precuneus plasticity, cognitive performance, plasma Aβ, plasma tau, as well as precuneus and hippocampal volumes. On Visit 1, participants will undergo a standardized battery of neuropsychological tasks and blood collection (for plasma Aβ, plasma tau, and APOE genotype). On both Visit 2 and Visit 3, the intermittent theta burst stimulation (iTBS)[33] will be applied over the precuneus to probe iTBS-evoked synaptic plasticity. Resting-state fMRI and resting-state EEG data will be acquired on Visit 2 and Visit 3, respectively, to evaluate iTBS-evoked measures of precuneus plasticity. On both Visits 2 and 3, participants will receive 3 consecutive sessions of iTBS with an inter-sessions interval of 60 minutes to maximize the iTBS probing effect[34,35]. Resting-state fMRI (Visit 2) and resting-state EEG (Visit 3) data will be collected immediately before and immediately after each iTBS session. Additionally, T1-weighted structural MPRAGE (for assessment of precuneus and hippocampal volume), and high-resolution hippocampal MRI (for volumetric measurements of hippocampal subfields) will be acquired before the interleaved iTBS-fMRI sessions on Visit 2. There will be a 2-week washout period between Visit 2 and Visit 3. The study design is illustrated in Figure 2.

**Proposed One-Year and Long-Term Outcomes:**

We plan to complete this project within 2 years. The first two months of the project will be devoted primarily to additional experimental design, preparation, and recruitment of participants; and the last 3 months will be devoted to data analyses and manuscript completion. During the intervening months, the research will proceed at the rate of 2-3 completed participants per month. The data we will acquire carrying out this project will prepare us to apply for an R01 grant. The NIH proposal we are planning to submit will involve implementing a longitudinal study that evaluates the longitudinal course of precuneus synaptic plasticity in preclinical and prodromal AD and its relationship with ATN biomarkers. We expect that findings of our proposed project in conjunction with other biomarkers will enhance our understanding of synaptic plasticity in preclinical and prodromal AD. Furthermore, findings of this project may contribute to more efficacious approaches to prevent and manage AD in the incipient stages of the disease.

**Year End Progress Summary:**

We have recruited 9 individuals with mild cognitive impairment (MCI) and 11 cognitively normal (CN) adults for our study. Comprehensive neuropsychological assessments have been administered to measure memory, executive functions, attention, processing speed, and language abilities. Additionally, we have collected structural and functional MRI data, along with EEG recordings. In accordance with C2N Diagnostics' guidelines[36,37], blood samples were obtained at the University of Arizona's Clinical and Translational Sciences Research Center. These plasma samples are deidentified and preserved in a frozen state at the University of Arizona's Health Science Biorepository. Upon aggregation of the additional samples, they will be dispatched to C2N Diagnostics for analysis, using express courier service with dry ice (Priority Overnight).

Recently, the MRI scanner at the University of Arizona has been fully booked until August 2024. We are actively coordinating with the Brain Imaging Center to explore options for additional time slots to accommodate scheduling for our research participants. Our aim is to conclude this project by June 2025.

Two manuscripts associated with this project have been accepted for publication, and another two are presently under peer review. Please refer to the list below for further details.

1. Hall, J.D. Green, J. M., Chen, A. Y., Liu, Y., Zhang, H., Sundman, M. H., & **Chou, Y.-H.** (in press). Exploring the potential of combining transcranial magnetic stimulation and electroencephalography to investigate mild cognitive impairment and Alzheimer's disease: A systematic review. *GeroScience*.
2. Sundman, M. H., De Vault, B. E. A., Chen, Y. A., Madhavan, L., Fuglevand, A. J., & **Chou, Y.-H.** (2023). The (hyper)excitable brain: What can a ubiquitous TMS measure reveal about cognitive aging? *Neurobiology of Aging, 132,* 250-252.
3. Sundman, M. H., Green, J., Fuglevand, A. J., & **Chou, Y.-H.** (2024). Characterizing the neurophysiological correlates of age-related cognitive decline with corticomotor transcranial magnetic stimulation. Manuscript submitted to *Aging Brain*.
4. Liu, Y., Sundman, M. H., Ugonna, C., Chen, A. Y., Green, J. M., Haaheim, L. G., Siu, H. M., & **Chou, Y.-H.** (2024). Reproducible routes: Reliably navigating the connectome to enrich brain stimulation strategies. Manuscript submitted to *Journal of Neurology*.

We profoundly appreciate the support from the Arizona Alzheimer's Consortium. Our newly submitted R01 grant, titled "Uncovering the Hidden Signs of Alzheimer's Disease: Advancing Assessments of Hyperexcitability, Cholinergic Dysfunction, and Impaired Plasticity Potential in

Preclinical and Prodromal Stages," an extension of the AAC Developmental Award project, has received an encouraging impact score of 37 at the 24th percentile. The proposed R01 project is designed to improve longitudinal disease monitoring and pave the way for developing targeted interventions. We intend to carefully address the reviewers' feedback and resubmit the grant in July or October 2024. The valuable data gathered through the AAC Developmental Award project will significantly enhance our resubmission of the R01 grant.

# ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Assessing Hippocampal-Prefrontal Communication During Memory Guided and Sensorimotor Behaviors Using a Transgenic Rodent Model of Alzheimer's Disease.**
Stephen L. Cowen, PhD, Carol A. Barnes, PhD, Abhilasha Vishwanath, MA, Gabriel Holguin, MA, Gabriel Winter, MA, Sahana V. Srivathsa, MA, Mauricio Serna, Helena Morrison, PhD, RN, Mitchell Barlett, PhD, Monica Chawla, PhD. Departments of Psychology, Nursing, and Surgery; University of Arizona; Arizona Alzheimer's Consortium.

**Specific Aims:**

Our working hypothesis is that the capacity of neurons in the hippocampus and prefrontal cortex for processing mnemonic and sensorimotor information will be reduced in the TgF344-AD rat model of Alzheimer's disease. Specifically, we predict that 1) the reliability of neural communication between hippocampal and prefrontal neurons will be disrupted in TgF344-AD rats (e.g., reduced inter-region cell-pair measure of correlation and shared variance) when animals must recall previous spatial locations during a maze-running task, and 2) that the capacity of neurons in the in the TgF344-AD animals to track changing sensorimotor input during track running and a novel string-pulling behavior will be impaired. While we will not perform a full between-group comparison in one-year, evidence that we can integrate Neuropixels recordings with high-speed video in TgF344-AD animals would be compelling data for planned NIA R01 proposals.

Aim 1: Interface the high-density Neuropixels system with a commutator to allow animals to behave freely on memory-guided and string-pulling tasks. We will synchronize Neuropixels measurements with high-speed video recording. Outcome measures include body and paw position and speed, cell stability, and the correlation between single-unit activity and behavior.

Aim 2: Compare measures of ensemble-level communication between prefrontal cortex and ventral hippocampus (e.g., cross-correlation) in control and TgF344-AD rats performing the W-maze and string-pulling tasks. Prediction: Neural communication and the capacity of neurons to process incoming sensorimotor information will be disrupted in the TgF344-AD animals.

**Background and Significance:**

Normal aging and Alzheimer's disease are associated with a decline in the ability neurons to respond promptly and reliably to inputs. This has significant consequences as millisecond-level coordination between ensembles of neurons is critical for learning and neural plasticity. While much research has investigated the impact of aging and Alzheimer's disease on the activities of individual neurons, less is known about how networks of neurons cooperate to process sensorimotor information and how this information is stored and retrieved. Sensorimotor slowing and memory impairment are key features of Alzheimer's disease.

To effectively assess coordination between neurons and their role in memory and decision making, it is necessary to measure the activities of large groups of neurons simultaneously. Combining such recordings with precise measurement of spatial/motor behaviors is critical for understanding how aging and disease affect neural coordination. Recent work from our group (Crown et al.1) has shown that many age-associated deficits in neural processing are only evident when single-unit and local-field activity is mapped onto specific features behavior (e.g., spatial location, running speed, and acceleration). The **objective of this proposal** is to build upon our success in implementing the Neuropixels system for high-density recording (Fig. 1) by coupling this system with hardware and software for high-speed video recording (350+ frames/second)

and deep-learning to investigate relationships between neural activity and spatial memory and sensorimotor input. Data will also be collected from the TgF344-AD rat model of Alzheimer's disease, so data will be of direct relevance to the study of Alzheimer's disease and its impact on neuronal processing. Acquired data will be foundational for a planned NIA R01 grant investigating communication between the hippocampus and prefrontal cortex and Alzheimer's disease.

**Preliminary Data, Experimental Design and Methods:**

**Neuropixels Recording System:** Because of the support provided by the Alzheimer's Consortium last year, we were able to implement the Neuropixels recording system in house. Using two probes, we measured the simultaneous activity of large ensembles of neurons in the medial prefrontal cortex and ventral hippocampus, regions involved in memory formation and planning. Separately, we developed a camera system for recording limb movements with unprecedented precision. Our goal is to integrate these systems.

**String-Pulling and W-Maze Tasks:** Previous work from our group (Crown et al.[1]) identified a clear age-associated decline in the capacity of neural activity in the hippocampus to track incoming sensorimotor and spatial information (e.g., speed, acceleration). This finding supports the need for precise measurement of behavior and synchronization with neural recording systems. To further analysis of behavior, we developed a novel string-pulling task and video/software system for measuring grasping behavior. Software we developed automatically segments of the reach and grasp movements. Our goal is to map these precise measurements with neural ensemble recording for the characterization of how neural processing of sensorimotor information and ensemble activity is impacted in the TgF344-AD model of Alzheimer's disease.

Spatial memory is impaired in aging humans and rats and spatial behaviors require the integrity of the hippocampus. We predict that spatial memory will be impaired in the TgF344-AD model. Tasks for spatial memory often pose problems for tethered recording systems as animals turn and tangle the recording tether. Prior to November 2022, no commutator (for untangling tethers) was available for the Neuropixels system, limiting the tasks we could use. Recently, a commutator became available (Doric Lens, Inc.) allowing us to record from TgF344-AD performing the established W-maze task of spatial sequence memory. Our group has preliminary data suggesting an age-associated impairment in this task.

**Experimental Designs and Methods:**

We will implant 2 F344 and 2 TgF344-AD (12 mo.) with Neuropixels probes in ventral hippocampus and medial prefrontal cortex. Recordings will be acquired during performance on the W-Maze and string-pulling tasks for 5 days. Implants will remain on the animal for >8 weeks to assess electrode stability.

**Proposed One-Year and Long-Term Outcomes:**

One-year: 1) Integrate the chronic recording Neuropixels system with a commutator and high-speed camera system. 2) Collect neural ensemble and behavioral data from TgF344-AD animals (2 model, 2 controls) as they perform the W-maze and string-pulling tasks. Data will support an NIA R01 grant application investigating hippocampal-prefrontal interactions in Alzheimer's disease. Timeline (months): 1-2) Assemble equipment. Validate commutator with test equipment. 2-4) Work out electronics for synchronizing video with Neuropixels. 4-6) Train animals on W and string-pulling tasks. 5-8) Record with the system. 7-11) 'Spike sort' data. 10-12) Analyze data and generate key figures for NIA R01.

**Year End Progress Summary:**

1. As specified in Aim 1, we successfully integrated neural recordings in the hippocampus from the high-density Neuropixels system with high-speed cameras (350 frames per second) for investigating the relationship between limb movement, neural activity, aging, and Alzheimer's disease. The methods for this approach have been recently published by our group in the Journal of Neuroscience Methods (Jordan et al., 2024). Our improved capacity to connect neural measurements with precise measures of motor control is important as motor control, balance, and memory are all impacted by aging and AD and there are notably strong relationships between memory-related activity in the hippocampus and movement. These data were collected by Gabriel Holguin (graduate student).
2. We have collected neural ensemble data from 7 healthy animals using the Neuropixels recording system as animals performed both spatial and string-pulling behaviors. We also measured activity during sleep. These data allowed us to refine and improve data analysis (e.g., Spike sorting and the analysis of movement as described in the proposal) and we now have a reliable data analysis pipeline for all future recordings. These data were collected by Gabriel Holguin (graduate student). Data collected exceeds our original goal of acquiring neural ensemble data from 4 animals over the funding period; however, these data were acquired from Sprague Dawley rats instead of the target TgF344-AD (Alzheimer's model) animals for reasons described below.
3. Challenge and workaround: Our original goal was to collect neural ensemble data from the hippocampus of 2 behaving control F344 and 2 TgF344-AD rats (a model of Alzheimer's disease). While we collected data from 7 rats, we were not able to collect data from the TgF344-AD animals we received from our collaborators in California. This was due to the poor behavior of these animals. Both control and TgF344-AD rats were unusually stressed and lacked motivation to perform even simple track-running behaviors, let alone the more complex W-maze working memory task described in the proposal. We attempted to train five TgF344 rats on this task without success. After consulting other research groups using these animals, we believe their poor performance was a result of transportation-related stress as these animals were moved from Missouri to California (for another research project) and then to Tucson. Furthermore, the F344 and TgF344-AD animals are known to be highly sensitive to stress. Given this and practical constraints (RRRC, the supplier of these animals, can only supply a very limited quantities of rats at unreliable intervals), we decided to establish a colony of rats in Tucson. A graduate student (Gabrial Winter), technician (Mauricio Serna), and collaborator (Mitch Bartlett) successfully established an independent colony of TgF344-AD rats at the University of Arizona. We have over 70 transgenic animals currently and are waiting for these animals to age to 6mo which is the target age for the time of electrode implantation. Animals not used for the project will be made available to the UA research community to advance local research in AD.
4. Aim 2: Collect neural ensemble data from the prefrontal cortex. We have collected data from the medial prefrontal cortex >10 anesthetized F344 rats using Neuropixels probes. These experiments involved stimulating the ventral hippocampus and measuring evoked neural responses from the prefrontal cortex to determine which regions of the frontal cortex receive the strongest input from the hippocampus. The goal of these experiments is to use these data to identify the optimal location in the mPFC for the implantation of electrodes in chronically behaving animals. These experiments revealed that the strongest derive from ventral hippocampus to prefrontal cortex is to the infralimbic region of the frontal cortex. These results will be published and have been presented at the 2023 Society for Neuroscience meeting. Sahana Srivathsa and Abhilasha Vishwanath (graduate students) led this project.
5. As specified in the proposal, we purchased a commutator for these experiments. A commutator is a device that improves the ability to measure neural activity while animals rotate during natural behaviors. We tested this system and encountered challenges as the signal to the Neuropixels system became corrupted after ~20 minutes of data collection. We believe this results

from noise introduced by the long cable that connects the commutator to the animal. We are working on reducing the size of the cable, but in the current set of experiments, we discovered that the animals could move freely enough without the commutator. This problem must still be resolved, however, as more complex behaviors will involve more rotations of the animal. These data were collected by Gabriel Holguin (graduate student).

6. Supply-chain and purchasing challenges: There were unforeseen delays in ordering some equipment, such as Neuropixels probes, given disagreements with the U of Arizona legal department and the contract with Imec (the Belgian supplier of the probes). This delayed ordering of the probes by 6 months. Fortunately, we had a reserve of probes, and we were able to continue with experiments. This issue appears to have been resolved as of 6/24/2024.

# ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Contribution of Endothelin Signaling to the Alzheimer's Disease-Related Cerebrovascular Dysfunction.** Josiane Fernandes da Silva, PhD, Paulo W. Pires, PhD. University of Arizona; Arizona Alzheimer's Consortium.

**Specific Aims:**

Perivascular Aβ accumulation induces cerebral microvascular dysfunction via an altered miRNA profile. We further hypothesize that ET-1-dependent microvascular dysfunction will lead to neurovascular impairment and cognitive decline in a mouse model of AD. We tested these hypotheses in the following 3 Aims:

Aim 1 – To determine changes in miRNA profiles of cerebral arteries of the *5x-FAD*, a mouse model early-onset AD, which are relevant for ET-1 signaling.
Aim 2 – To determine the participation of ET-1 in microvascular observed in *5x-FAD*.
Aim 3 – To identify ET-1 antagonists as putative therapies to slow progression of cognitive decline and neurovascular reactivity in 5x-FAD.

**Background and Significance:**

Cerebrovascular alterations occur in Alzheimer's disease (AD) patients, likely a consequence of amyloid-β (Aβ) accumulation around brain blood vessels, resulting in cerebral amyloid angiopathy. Dysregulation of the cerebral microcirculation can impair vital mechanisms regulating real-time substrate delivery to the brain, consequently disrupting homeostasis within the neuron's microenvironment. Endothelin type 1 (ET-1) is an endogenously- secreted peptide that acts through endothelin receptor type A (ETAR) and type B (ETBR) to induce vascular constriction. Moreover, ET-1 is involved in vascular inflammation and oxidative damage. Exacerbated ET-1 production is linked to cardiovascular diseases, such as hypertension, and it may play an important role in AD-related vascular dysfunction. Several studies support the hypothesis that endothelin signaling is dysregulated in AD. For instance, ET-1 mRNA was found to be upregulated on the temporal neocortex of AD human and Aβ(1-42) stimulated ET-1 production in cultured human neuroblastoma cells. Additionally, Aβ potentiates the vasoconstrictor effects of ET-1 in human cerebral arteries. Furthermore, circulating ET-1 levels are higher in a mouse model of AD than in their controls. Together, these studies identify ET-1 as an important mediator on AD-related disorders; however, the evidence is associative and underlying mechanisms remain unknown. This proposal will fill this knowledge gap by providing a direct link between AD-induced excessive ET-1 signaling and cerebral microvascular dysfunction with mechanistic insight. Further, experiments delineated here will provide direct evidence to repurpose FDA-approved ET-1 antagonists as putative therapies to slow AD progression in patients. Endogenous regulation of ET-1 bioavailability can occur at the transcriptomic level by regulating expression of the ET-1 gene (EDN1). Moreover, several microRNAs (miRNAs) have been identified as potential modulators of ET-1 mRNA. miRNAs are small, non-coding RNA that can increase or decrease mRNA expression by affecting genomic regulation of gene expression. Alteration of miRNAs expression is associated with several pathological processes, including AD. However, whether AD-related changes in vascular miRNA profiles lead to upregulation of ET-1 signaling remains unclear. Completion of the proposed studies will identify the role of miRNAs in regulating ET-1 expression in the cerebral microvasculature during AD and may yield yet novel targets for therapeutic intervention.

**Proposed One-Year and Long-Term Outcomes:**

The findings that were obtained on this project will support the writing of a grant proposal for understanding how the endothelin signaling pathway can contribute to vascular dysfunction associated with AD. Moreover, the results obtained in aim 1 will be submitted, as a manuscript, to a peer reviewer journal in the end semester. Additionally, the results obtained here will also be presented at the 2024 Arizona Alzheimer's Consortium Scientific Conference, in September 2024. The long-term outcome is submitting a research grant proposal for AARG-D research grant on 2024 and for the 2025 Career Development Award on the AHA.

**Preliminary Data:**

We have reported that pial artery from *5x-FAD* mice, a mouse model early-onset AD showed higher vasoconstriction response to ET-1, using pressure myography system. Also, we showed that those mice have an impairment in neurovascular response to hyperemia, using the laser speckle contrast imaging system.

**Experimental Designs and Methods:**

To accomplish the aim1, we run a sub-transcriptome on pial arteries from male and female wild-type and *5x-FAD* mice, using CVD mRNA panel (800 mRNA) and miRNA panel (599 miRNA) from NanoString company. On those panels, it was included RNA related to endothelin signaling and also RNA that have already been describing to participate in vascular (dys)function. We also have validated panel results using qPCR methods for the following genes: ET-1, endothelin receptors type A and B. For aim 2, using pressure myography, we completed the preliminary data, characterizing the contractile response to ET-1 in cerebral pial artery and parenchymal arteriole. Moreover, we evaluated the effect of 10μM bosentan, ET-1 receptor antagonist, on the myogenic reactivity in response to intraluminal pressure curve. For aim 3, we concluded the baseline perfusion and neurovascular response to hyperemia experiments in wild-type and *5x-FAD* mice. Unfortunately, we did not have enough mice to initiate the *in vivo* treatment with bosentan, as was planned. However, those experiments are scheduled to be performed soon.

**Year End Progress Summary:**

**Aim 1 -** With the pilot grant support, we run the mRNA and miRNA panels on the cerebral pial arteries from WT and *5x-FAD* mice. From the 800-mRNA tested, in AD mice were found 15 upregulated and 20 downregulated genes. It is interesting to note that Edn1 mRNA, which codes pre-pro-ET-1, was downregulated and no change was observed in ET-1 receptor A or B. However, gene related to protein kinase and RAS signaling, such as Rasgrp1, Rapgef4 and Prkacb, were found up-regulated. Those genes play a role in regulating intracellular signaling, and they may modify ET-1 vascular response. It is important to point out that was observed a gender effect on the different expressed gene (DEGs) profile. Considering only female mice, it was found 72 DEGs in AD, being 16 upregulated and 56 downregulated. On the other hand, in male mice, only 5 DEGs were observed, 2 upregulated and 3 downregulated. End-1 mRNA was reduced only in female *5x-FAD* mice. Regarding miRNA expression, from the 599-miRNA tested, we found 13 miRNAs altered, being 7 downregulated and 6 upregulated. We also observed a gender effect on the result, since no miRNA was different expressed in male AD mice and 14 miRNAs were changed in female AD mice. Moreover, miRNA validated to regulate End-1, such as miR-206, was unchanged. However, miRNA that regulates intracellular kinases and phosphatase was found statistically upregulated, such as mmu-miR-434-3p. Those findings suggest that the hypercontractility to ET-1 could be related to a higher intracellular mechanism sensitivity rather than to change in ET-1 or ET receptors. However, we intend to quantify ET-1

and ET-3 by ELISA, even though we did not observe difference in RNA level, but the protein level could be altered by post-transcriptional /translational regulation.

**Aim 2 -** Vascular studies showed that both cerebral pial arteries and parenchymal arteriole from *5x-FAD* mice have higher spontaneous myogenic tone and contractile response to 30nM ET-1. Moreover, pre-incubation with 10μM Bosentan abolished the ET-1 vasoconstriction response in both WT and *5x- FAD* mice. Additionally, 10μM Bosentan reduced the myogenic tone during intraluminal pressure curve in WT but not in *5x-FAD* mice. This response was observed in both pial artery and parenchymal arteriole, suggesting in AD mice, an intrinsic ET receptor effect was lost.

**Aim 3 –** Our preliminary data of neurovascular reactivity was confirmed with the increment in the number of animals by experimental group. Both male and female *5x-FAD* mice have an impairment in the neurovascular response to hyperemia without change in basal cortical brain perfusion.

# ARIZONA ALZHEIMER'S CONSORTIUM
# 2023-2024 SCIENTIFIC Project Description

**Development of Small Molecule Selective $OX_1R$ Agonist & Dual $OX_1R/OX_2R$ Agonist to Explore the Role of Orexin System in Alzheimer's Pathology.** Kevin Gaffney, PhD, Kathleen Rodgers, PhD. University of Arizona Center for Innovation in Brain Science; Arizona Alzheimer's Consortium.

**Specific Aims:** In *Specific Aim 1*, we will generate a number of analogs of two promising orexin receptor (OXR) agonists hits CIBS-003 and CIBS-017 (**Fig. 1**), identified during our previous AAC proposal. We will also synthesize a series of molecular hybrids between these hits and dual $OX_1R/OX_2R$ antagonists (suvorexant, filorexant, and SB-649568),[1] selective $OX_1R$ antagonist (JNJ-61393215),[2] and selective $OX_2R$ agonist TAK-925[3] (**Fig. 2**) to leverage the potency of these existing OXR modulators. We will then test the agonist activity of these newly synthesized compounds on both $OX_1R$ and $OX_2R$ and model these compounds on both receptors using molecular dynamics simulations to explore the structure activity relationship (SAR) of our novel small molecule orexin agonists. We will then use those insights to develop potent, non-cytotoxic a selective $OX_1R$ agonist and a dual $OX_1R/OX_2R$ agonist.

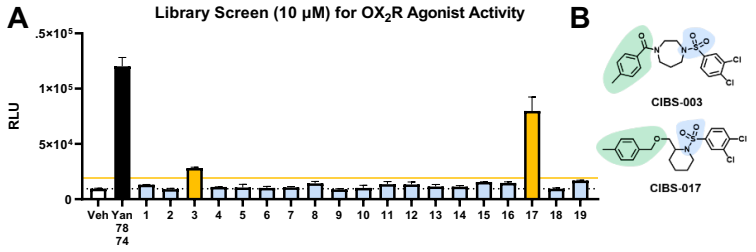


**Figure 1.** (**A**) Screening of custom, proprietary small molecule $OX_1R/OX_2R$-targeting agonist array in pan Gα $OX_2R$ assay identified two hits (**B**) CIBS-003 and CIBS-017.

**Preliminary Data:**

During our previous AAC application, we successfully: i) synthesized a focused dual OXR-targeting array, ii) screened this array for $OX_2R$ activity, and iii) identified two novel OXR agonists. (**Fig 1**).

**Background and Significance:**

One of the symptomatic hallmarks of Alzheimer's disease (AD) is sleep disturbances.[4] Sleep impairment is increasingly seen as a marker of the prodromal, mild-cognitive impairment phase of AD.[5] During sleep, there is an increase in cerebrospinal fluid flow which removes toxic metabolites and waste from the brain.[6] Further, sleep deprivation has been shown to increase CNS levels of amyloid β (Aβ) and tau.[7,8] Sleep is modulated in part by the activation of the $OX_2R$ by their ligands orexins A and B. In the Tg2576 AD mouse model, treatment with dual $OX_1R/OX_2R$ antagonist almorexant decreased Aβ levels and Aβ plaque formation.[7]

Interestingly, orexin peptides have been shown to be neuroprotective, primarily through the $OX_1R$, in models of AD, age-related cognitive decline, and Parkinson's.[9,10,11] Taken together, we *hypothesize* that the elevated orexin levels in early AD are attempts by the brain to prevent degeneration and that small molecule orexin receptor agonists would decrease pathology in AD. In order to test this hypothesis, in this proposal, we seek to build upon our the success of our 2019-2020 AAC proposal by: (i) better understanding the $OX_1R$ and $OX_2R$ SAR of a focused series of CIBS-003 and CIBS-017 analogs; (ii) use these insights to develop potent, non-cytotoxic a selective $OX_1R$ agonist and a dual $OX_1R/OX_2R$ agonist. The successful completion of these goals will allow us to compare the efficacy of selective $OX_1R$ activation to dual $OX_1R/OX_2R$ in pre-clinical models of AD.

**Experimental Designs and Methods:**

*Approach*: When we started our work on OXRs, two series of small molecule OXR agonists had been reported which are exemplified by Yan7874 (weak & cytotoxic) and YNT-185 ($OX_2R$ selective).[12,13] In contrast, numerous OXR antagonists had been developed (for the treatment of insomnia). Both the agonists and antagonist contain hydrophobic motifs (green & yellow) and a ringed linker, but the antagonists lacked the non-planar hydrogen bond acceptor (blue) of Yan7874 and YNT-185, and TAK-925, recently (2022) reported (**Fig. 2B**). Based on this analysis, we designed molecular hybrids that added motifs (such as the sulfonamide and hydroxyl) from the agonists Yan7874 and YNT-185 to the scaffolds of dual $OX_1R/OX_2R$ antagonists. We then synthesized a custom, proprietary small molecule $OX_1R/OX_2R$-targeting agonist array, screened these compounds for $OX_2R$ activity, and identified two promising hits, CIBS-003 & CIBS-017.

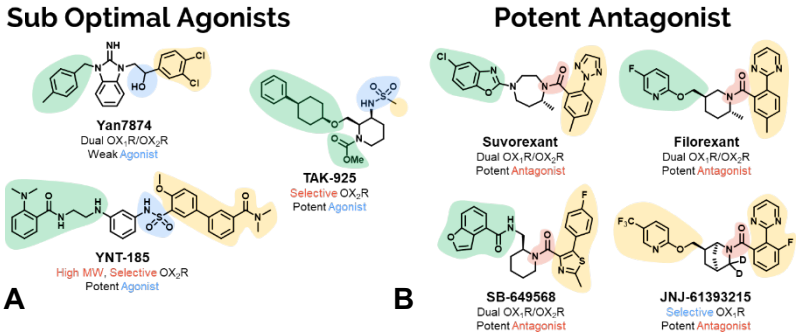


**Figure 2.** Structural comparison of OXR agonists and dual $OX_1R/OX_2R$

The work of this proposal seeks to improve the potency CIBS-003 and CIBS-017 through two approaches (**Fig. 3**). First, we will focus our medicinal chemistry efforts on synthesizing a number of analogs of these two promising hits. Second, we will leverage the wealth of OXR antagonist SAR a series of molecular hybrids between these hits and selective $OX_1R$ antagonists or dual $OX_1R/OX_2R$ antagonists (**Fig. 2**) to rapidly increase OXR potency of our hits. The activity of each round analogs will inform the design and synthesis of subsequent generations of more potent analogs which will be optimized for their "drug-likeness" ultimately resulting in our lead $OX_1R$ and dual $OX_1R/OX_2R$ agonists. Select compounds will be tested for *in vitro* eADME (microsomal stability, permeability, and cytotoxicity) to ensure its suitability for use as *in vivo* probes.

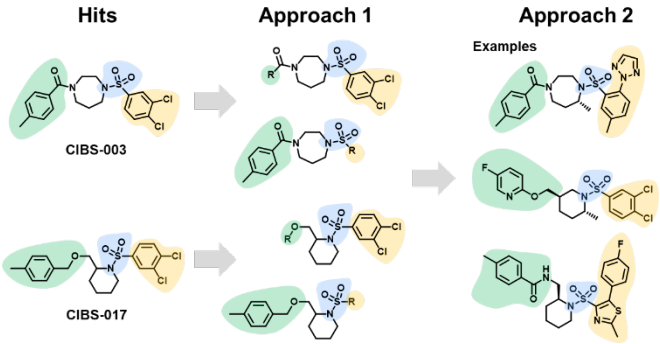


**Figure 3.** Overview of our 2 approaches to rapidly improve our promising

*Synthesis:* Our proposed analogs will be synthesized according to published reports.[13,14,15] Based on the SAR, we will be design subsequent generations using the software suite from Schrodinger LLC.

*$OX_1R/OX_2R$ & Drug-likeness Assays:* The synthesized molecules will be assayed in CHO-K1 cells over-expressing either $OX_1R$ or $OX_2R$ to assess their ability to agonize either receptor, as measured by $Ca^{2+}$ mobilization. For agonists of interest, a 10-point dose response will be determined to determine $EC_{50}$. For molecules of interest that do not produce an agonist response, their ability to antagonize the actions of orexin B on either $OX_1R$ or $OX_2R$. Following the development of a "lead-like" dual $OX_1R/OX_2R$ agonist, this molecule will be passed through a number of *in vitro* assays to ensure its suitability for use as an *in vivo* probe: microsomal stability, permeability, and cytotoxicity.

**Proposed One-Year and Long-Term Outcomes:**

During our previous AAC application, we successfully: i) synthesized a focused dual $OX_1R/OX_2R$-targeting array, ii) screened this array for $OX_2R$ activity, and iii) identified two novel OXR agonists. Unfortunately, the synthesis and screening of this array compounds consumed the entirety of the time and budget of this previous proposal. While CIBS-003 and CIBS-017 represent promising hits, additional improvements in potency will greatly increase our chances of receiving NIH and/or DoD funding. This assessment is based on our previously experience in successfully advancing an AAC-funded program into two funded Phase 1 SBIRs, including one AD-focused application. Consequently, this proposal seeks to leverage the $OX_1R/OX_2R$ toolkit we developed during our previous AAC proposal to carry out the necessary medicinal chemistry on our promising hits to improve their $OX_1R/OX_2R$ activity. Results from this 2023-2024 proposal will provide the preliminary data necessary to pursue NIH and/or DoD funding and industry and investor support. Crucially, data and findings from this proposed project will be submitted for presentation at relevant scientific conferences and in peer-reviewed manuscripts.

# ARIZONA ALZHEIMER'S CONSORTIUM
# 2023-2024 Scientific Progress Report

**Neural Correlates of Age-Related Alterations in Imaginative Thinking.** Matthew D. Grilli, PhD, Jessica R. Andrews-Hanna, PhD, Mariam Hovhannisyan, MA, Matthew Huentelman, PhD, Steven Rapcsak, MD. University of Arizona; Translational Genomics Research Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

## Specific Aims:

**Aim 1**: To determine the forms of imaginative thought (i.e., mind's mind and mind's eye) present in autobiographical memory in younger and older adults. **H1:** Older adults will have more mind's mind details in their autobiographical memories, whereas young adults will have more mind's eye details.

**Aim 2**: To determine the underlying neural correlates of different forms of imaginative thought and autobiographical memory in younger and older adults. **H1**: Functional connectivity within the DN-MTL subsystem will be greater in younger relative to older adults during visualize trials (where participants are instructed to visualize objects). In contrast, functional connectivity within the DN-dMPFC subsystem will be greater in older relative to younger adults in the categorize trials (where participants are instructed to name semantic categories). **H2:** Older adults will show weaker functional connectivity in the DN-MTL subsystem and greater functional connectivity in DN-dMPFC subsystem for a novel autobiographical memory task, where they are asked to retrieve a memory with the item shown to them.

**Exploratory Aim:** To assess whether APOE4 status modulates task-based functional connectivity in the DN-dMPFC or DN-MTL subsystems while engaged in imaginative cognition.

## Background and Significance:

Normal aging and higher risk for AD are associated with alterations in imaginative cognition. However, what distinguishes normal aging from higher AD risk in the patterns of imaginative thoughts remains uncertain. We recently proposed a novel neuroscience-informed theoretical model of imaginative thought that centers on the mechanisms of the DN[5]. Through the lens of this model, we can examine how two subsystems of the DN support imaginative thought, potentially revealing similarities and differences in the cognitive features and neural correlates of autobiographical memories generated by young and cognitively normal older adults. We can also begin to explore whether a subsystem framework can detect cognitive and neural signatures of higher risk for AD among cognitively normal older adults, as examined by APOE4 and plasma biomarkers of amyloid, tau, and neuroinflammation.

The significance of our project is highlighted by its potential to 1) be the first to provide evidence that the two subsystem profile of the DN underlies two distinct subtypes of imaginative thought, which we have referred to as the mind's eye and the mind's mind, 2) offer a novel theory and scoring protocol to move research forward on aging and imaginative cognition, and 3) reveal evidence that normal aging and higher AD risk have distinct signatures of DN functional connectivity while engaged in imaginative cognition – an outcome that could galvanize further research on separating adaptive from maladaptive age-related differences.

## Preliminary Data, Experimental Design and Methods:

Preliminary data from our lab has shown that cognitively normal older adults tend to share less specific autobiographical memories than younger adults[1,5,20]. We have also shown in several data sets that positive APOE4 status among cognitively normal older adults is associated with lower

memory specificity[1,5,14,19,20]. Over the past year, we have created and established high reliability for a novel scoring protocol for imaginative thought. Using this protocol on a preliminary data set, we have found that younger adults share more mind's eye details in their autobiographical memories, whereas older adults share more mind's mind details. Preliminary data from our lab has also shown that individual differences in autobiographical memory specificity is associated with variability in the integrity of the DN, in particular the DN-MTL subsystem.

**Proposed One-Year and Long-Term Outcomes:**

One-year outcomes: Enroll 20 young adults and 20 older adults in the study, put together an analytical plan to submit as a pre-registered study, and begin data cleaning. Long-term outcomes: Incorporate these data with an ongoing R01 study that involves naturalistic assessment and plasma biomarkers that will be analyzed in Year 3 and Year 5 of the paired R01 and serve as key findings for a NRSA application submitted by Co-I Hovhannisyan.

**Year End Progress Summary:**

Regarding Aim 1, we successfully developed and validated a scoring protocol to assess imaginative thoughts in young and older adults in two different forms of imaginative thinking (past and future thinking). The scoring protocol was developed based on a neurocognitive framework of imagination that posits that the mind's eye (concrete, image-based form of imagination) and the mind's mind (abstract, verbal-based form of imagination) are supported by the brain's default network. In addition to the development of the scoring protocol, we also applied this scoring protocol to data in young and older adults across two separate studies and have submitted that project for publication. The preprint can be viewed here: https://osf.io/preprints/osf/gyrz9. Revisions on this manuscript were recently requested and we are nearly finished responding to the reviews. To summarize, there were three main findings from this study. First, we showed that young and older adults differ in their imaginative thinking such that older adults exemplify more mind's mind elements in their thoughts compared to young adults, in line with our hypotheses. Second, this study also revealed that within the older adult cohort, imaginative thinking did not change with older age. Lastly, we found that older adults expressed less self-related thoughts compared to young adults. These findings contribute to our understanding of how different forms of imaginative thinking change with age. Given that the scoring protocol has excellent interrater reliability and can be applied to different forms of thinking, we also applied it to other datasets in our labs examining various forms of thinking such as resting state cognition, autobiographical memory, and future thinking. Currently, we are examining what aspects of the default network support mind's eye and mind's mind form of imaginative thought. We presented this data at multiple conferences over the past year, including the Arizona Alzheimer's Consortium conference and the International Neuropsychological Society Annual Meeting. This project is directly related to the long-term research goals for Co-I Hovhannisyan's planned NRSA submission, as well as our team's R01 study that examines cognitive changes in aging in naturalistic settings. The reliable scoring protocol will allow us to examine these different forms of cognition in naturalistic settings. We have also discussed future projects to assess imaginative thinking in clinical populations to further assess our neurocognitive theory.

Regarding Aim 2, we successfully developed a novel fMRI task to examine age-related changes in different forms of imaginative thinking. We designed a novel psychological experiment to assess abstract and concrete forms of imaginative thinking. We developed and piloted this study in 7 participants before running the task at the MRI scanner. Our study conducts a rigorous three-step screening process to ensure that participants do not have contraindications for the MRI

scanner and are cognitively normal. Thirty-three participants made it to the final stage of the screening process and 20 of those participants were eligible and thus recruited as participants in the study. Thus far, 13 young adults and 7 older adults have completed the fMRI task in the scanner. Data cleaning is currently in process for all participants. Preliminary analyses in single subjects shows consistent effects with our hypotheses, including fMRI activity within the DN-MTL subsystem during the visualize task and fMRI activity within the DN-dMPFC subsystem during the categorize task. Related to our short-term goals, age comparisons and group level analyses have not been conducted yet as we are currently drafting a preregistration for this study. The analytical plan for the current study involves examining functional connectivity in the DN-MTL and DN-dMPFC subsystems as it relates to the visualize and categorize trials. Related to the exploratory aim and as part of our analytical plan, we also plan to examine whether APOE status plays a role in functional connectivity in the DN-dMPFC subsystem in older adults. In addition, data related to Aim 2 will be analyzed and presented at the next Arizona Alzheimer's Consortium conference. Related to the long-term outcomes, this study has been incorporated as part of an ongoing R01 grant and will continue to recruit participants. This study will be analyzed in conjunction with the other naturalistic assessment and biomarker data to provide pilot data for an NRSA application submitted by Co-I Hovhannisyan.

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Pilot Study on the Safety and Efficacy of Angiotensin (1-7) for Cognitive Impairment in Heart Failure Patients at Risk for Vascular Dementia and Alzheimer's Disease Related Dementias.** Meredith Hay, PhD, Lee Ryan, PhD, Christina Hoyer-Kimura, PhD, Justin Palmer, Radha Gopalan, MD, Kristian Doyle, PhD, Jennifer Frye, Elizabeth Juneman, MD, Kristina Irwin, Angelica Galdamez-Avila, Karina Carrillo, Sobeyda Lizzette Cruz, RN, Cindy Schrag, Suzanne Oskouie, MD, Anantharam Kayla, MD, Arianna Bedoya, MPH, John Konkilas, PhD, Nancy K. Sweitzer, MD. University of Arizona; Washington University, School of Medicine; Sarver Heart Center; Evelyn F. McKnight Brain Institute; Banner Health, Tucson; Banner Health, Phoenix; Arizona Alzheimer's Consortium.

**Specific Aims:**

1) Establish the baseline and 12-month change in NfL values in HF patients at risk for VCID/ADRD and determine the association between absolute levels and changes in NfL with measures of cognitive function and brain MRI findings in subjects with symptomatic HF.
2) Determine if 12 weeks of treatment with Ang-(1-7) in HF patients at risk for VCID/ADRD improves cognitive functions measured as a change in performance from baseline to follow up on composite scores of memory, executive functioning, language and processing speed in the Ang-(1-7) treatment groups compared to placebo controls.
3) Establish if treatment with Ang-(1-7) modifies the absolute levels of plasma NfL and the change in the values over 12-months.

**Experimental Design and Methods:**

Individuals with II-IV stage (NYHA) heart failure who were 50 years and older were enrolled. Baseline and 12-month cognitive function was determined in HF patients at risk for VCID/ADRD via a compressive battery of neuropsychological and functional tests, including Face Name (FNAME), Verbal Paired Associates (VPA), Keep Track, Rey Auditory Learning Test (AVLT), Mnemonic Similarity Task (MST), Number Letter, Flanker, Deary, Montreal Cognitive Assessment (MoCA), and North American Adult Reading Test (NAART). Serum samples were taken from participants following cognitive battery and tested for blood levels of neurodegenerative biomarkers (NfL, pTau 181 via Quanterix Simoa) and cytokines (Milliplex Assay). We will use blood biomarker levels of neurodegenerative, cytokines, and heart failure (NT-proBNP) to assess the association of biomarkers with measures of cognitive function and to determine whether baseline levels of NfL predict change in cognitive function over a 12-month period. Following baseline assessments of cognitive function and blood collection, subjects who have consented to participate in the Ang-(1-7) sub-study and have will be chosen and randomly assigned to be given either Ang-(1-7) (100 micrograms/kg/day via subcutaneous injection) for 90 days or saline placebo.

**Proposed One-Year and Long-Term Outcomes:**

Our One-Year outcome for this study is to provide early proof-of-concept clinical trial data that will support a larger, more comprehensive NIH-funded study on the safety and efficacy of Ang (1-7) to prevent cognitive impairment in HF patients at risk for developing VCID/ADRD.

Our Long-Term outcome is to demonstrate whether plasma NfL exhibits characteristics that make it useful as a Prognostic Biomarker to predict cognitive decline in early heart disease-associated VCID and identify pre-VCID-symptomatic in individuals with symptomatic HF. Our goal will be to use levels of plasma NfL as an enrollment enrichment factor in future trials to allow

enrollment or stratification of patients more likely to develop VCID or ADRD and be responsive to Ang-(1-7) therapy.

**Year-End Progress Summary:**

The following is a summary of our activities on the proposed one-year outcomes. The study has been closed to enrolments, and preliminary biomarkers and cognitive function data are being analyzed and compiled for publication.

Setbacks over the last 12 months included lack of cardiologists in the HF clinic at the TUS and PHX sites to participate in recruitment and the subsequent decline in recruitment from the Tucson and Phoenix, and multiple declines to return for 12-month follow-up have limited studies' ability to assess longitudinal changes in biomarkers, cognitive performance, and Ang-(1-7) efficacy.

Over the last year, we have had the following:

2476: total # of subjects prescreened
225: total # of subjects that met the criteria
4: total # of subjects consented
2: total # of subjects enrolled.

At Study close, we had the following:

8279: total # of subjects prescreened
1282: total # of subjects that met the criteria
45: total # of subjects consented
34: total # of subjects enrolled, (including withdrawn participants).

During the last year, the following has been performed:

- IRB approved study closeout 1/19/2024
- Filed for IRB extension to finish out data analysis
- Finished the last patient receiving drug/placebo (n=4)
- Closed study enrollment and closed out all active participants. Final participants were contacted on 2/26/2024

Biomarker arm- preliminary findings:

HF subjects (n=34, mean age 68, 38% female) were recruited from the Banner-University cardiology clinics in Tucson and Phoenix and compared to healthy control samples (n=32, mean age 64.50, 62% female). A cognitive composite score was calculated from the averaged z-scores from the administered Verbal Paired Associates Total, Face-Name Test components, and Keep track. HF individuals had significantly impaired cognitive function (Mann-Whitney, $p<0.0001$).

Serum NfL ($p=0.023$), pTau181 ($p=0.042$), IL-6 ($p=0.002$), IL-7 ($p=0.030$), IL-10 ($p=0.0051$), IL-12p40 ($p=0.0005$), IL-15 ($p=0.042$), and TNFα ($p=0.010$) were significantly increased in individuals with HF compared to healthy controls. Levels of NfL, IL-6, and TNFα negatively correlated with cognitive abilities. To determine if a combination of biomarker scores could predict cognitive impairment, a calculated cognitive score was derived from the arithmetic combination of calculated NfL, NT-proBNP, IL-6, and TNFα raw measured value via Score=(NfL+NT-proBNP)(IL6+TNFa).

*Conclusion:* These findings suggest that cognitive impairment in patients with HF may be predicted using a combination of neurodegeneration, inflammatory, and cardiac function plasma biomarkers and may be useful in identifying individuals that may benefit from cognitive protective therapies.

Drug arm- preliminary findings:

For the investigational drug arm of our study, we enrolled 4 individuals either given Ang-(1-7) or saline as control. N=2 (50% female, average age 59.5, average education 15.5) received Ang1-

7, and n=2 (0% female, average age 62.5, average education14.5) received a placebo. All participants were contacted via weekly phone calls during which adverse effects where recorded.

*Safety:* No adverse events were recorded for any participants receiving Ang (1-7).

*Conclusion:* No adverse events were noted in the small population following Ang (1-7) treatment. No cognitive outcomes could be determined in the current study population.

## ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Microstructural MRI Mapping of Hippocampal and Brain Stem Substructures in the Bonnet Macaque Brain During Aging.** Elizabeth Hutchinson, PhD, Carol Barnes, PhD, Ted Trouard, PhD, Kelsey McDermott, Laurel Dieckhaus. University of Arizona; Arizona Alzheimer's Consortium.

**Specific Aims:**

**Specific Aim 1:** Imaging substructures of the brainstem and hippocampus in the aged Bonnet Macaque brain.

**Specific Aim 2:** Probing neurite and cell density with advanced diffusion encoding.

**Background and Significance:**

The hippocampus, cerebral white matter and some brainstem regions are preferentially vulnerable in age-related disorders with cellular and molecular underpinnings that may be accessible to microstructural MRI techniques. In the hippocampus, the perforant path axons that project from the medial entorhinal cortex to the dentate granule cells undergo axon collateral pruning during healthy aging without cell loss, while the Schafer collaterals do not. While the effect of this pruning may have MRI correlates in human MRI and DTI studies, there is not a direct MRI marker for age-related pruning in the hippocampal subfields. We expect that microstructural MRI will be sensitive to these subtle alterations using high-resolution MRI of anatomical substructures and advanced diffusion encoding techniques, especially QTI.

*Ex vivo* MRI or 'MRI microscopy' has superior sensitivity and resolution compared to *in vivo* MRI and has recently been appreciated as an important ancillary method to combine with higher-resolution histological studies to provide novel opportunities to study the microstructural condition of previously unobservable white matter projections, particularly those originating in subcortical brain regions in the midbrain and brainstem, which are notoriously difficult to resolve and of small gray matter regions such as the hippocampal subfields, which are undergo well characterized pathologic changes in Alzheimer's disease. Because these regions sustain age-associated changes in structure and function relatively early in the aging progression, a quantitative assessment of microstructural associations with aging and cognitive status confirmed by comparison with cell-level changes is timely and an important problem.

**Preliminary Data:**

During the past project periods of AAC funding, we have collected high-resolution, whole brain images and microstructural MRI maps in a set of 12 bonnet macaque brains from animals with a long research history and age range of 12-32 years. Additionally, two of these brains have been serially sectioned and stained both for histologic study and for radiologic-pathological correspondence studies. Microstructural MRI maps – diffusion tensor imaging (DTI), mean apparent propagator MRI (MAP-MRI), bound pool fraction (BPF) and myelin water fraction (MWF) – have been successfully processed, modeled and registered to a common template space for the voxelwise and ROI-based evaluation of age-dependence of these metrics and for metric comparisons across microstructural MRI modalities. Tractography of the projections of the LC has also been performed and the expected remaining milestones of the present project period include tract-based spatial statistics analysis of white matter microstructure across age and between MRI metrics, quantitative characterization of the LC projections with respect to age and in comparison with histologic outcomes in the two sectioned brains.

**Experimental Designs and Methods:**

*Experimental Design.* Following a brief methods development phase to optimize local MRI scanning and QTI for this project, 6 bonnet macaque brains from two different age ranges (15-25, n=3; 25-32, n=3) will each undergo local MRI scanning of the temporal lobe and the brainstem using the pre-clinical 7T Bruker MRI system in the TBIR at UA.

*Aim 1 Methods.* In order to collect high-resolution MRI scans of the brainstem and hippocampus without the need to dissect the whole brain specimens, local surface receive coils – e.g. mouse/rat head coil or single loop coil – will be positioned on the surface of the brain using a 3D printed sample and coil holder. During a development phase, the holder will be built and different coils and geometries evaluated to determine the optimal experimental arrangement. This setup will be used to collect high-resolution anatomical (multi-echo T2W) and multi-shell diffusion MRI. Substructure visualization, ROI analysis and tractography will be performed to evaluate the age-dependence of microstructural MRI metrics in the hippocampal and brainstem substructures.

*Aim 2 Methods.* In the same scan sessions as described above, we will collect QTI scans from the hippocampus and brainstem. During the development phase, we will adapt our established protocols for QTI in fixed tissue for optimal contrast in the local bonnet macaque brain scans and during the data acquisition phase, we will collect and analyze QTI data along with the other protocols. We will compare QTI contrast images with the DTI and MAP-MRI metrics to better understand the capabilities of this method and evaluate all metrics in the LC and hippocampal subfields to determine if they report age-related alterations.

**Proposed One-Year and Long-Term Outcomes:**

*One Year outcomes*. The experiments of this proposal are expected to bring to completion our initial studies of advanced microstructural MRI in the aging bonnet macaque brain. Targeted, high-resolution analysis of two brain regions important for aging will finalize our observations in the whole brain and increase the impact of both the expected seminal publications of our work and the funding proposals that will build on their foundation. Specifically, in FY24 we expect:

- Optimization of local MRI and QTI protocols (Summer/Fall 2023, Hutchinson Lab)
- Collection of brainstem and hippocampus MRI scans (Fall 2023/Spring 2024, Hutchinson Lab)
- Analysis of substructure MRI outcomes including comparative metric analysis, age-dependence evaluation (Hutchinson Lab)
- High-resolution analysis of tractography and cellularity-related metrics in the LC (Barnes Lab)
- Behavioral correspondence studies (Barnes Lab)
- Presentation of results at ADRC, BME expo, SfN and ISMRM conferences.
- One publication related to advanced microstructural metrics.
- One publication, subsequent to above related to the LC projections and cellularity.
- R21-level grant submission in Fall 2023 and/or R01-level submission planned for post-publication.

*Long-term outcomes.* The long-term impact of this work is to define new microstructural MRI markers of healthy and diseased aging and to advance knowledge of the spatio-temporal trajectory age-related brain alterations. This proposal is a critical step in the research and funding pathways to advance this progress.

**Year End Progress Summary:**

1. Development and implementation of local Diffusion MRI. Whole Bonnet Macaque brain preparation with local imaging coils was optimized to enable imaging of the brainstem region at high resolution without dissection of the tissue. Single loop MRI receive coils were determined to yield the best image quality and consistent positioning of the specimens within the MRI scanner hardware was accomplished. Acquisition of MRI scans from the 6 brain specimens proposed was accomplished and diffusion MRI maps have been reconstructed. An additional MRI scan was developed to directly visualize the LC in these specimens using a selective inversion recovery T1-weighted protocol. Subsequently, this has been used to implement high-resolution tractography in the brain stem along with detailed metric mapping of microstructural features.
2. Analysis of microstructural MRI metrics and correlation with age. In order to improve on template-based ROI analysis in previous periods, we used a voxelwise binary classifier to identify aged-related changes in a bias free manner. For each voxel in the brain, the accuracy of predicting aged versus adult was calculated from diffusion-only MRI metrics, relaxometry-only MRI metrics and all metrics. Brain areas that showed significant differences included the thalamus, hippocampus, and amygdala and we found that the diffusion MRI metrics were the most influential for prediction accuracy.
   - This work was submitted for presentation at the 2024 Society for Neuroscience meeting.
   - This work is in preparation as a manuscript, expected to be submitted within the next year.
3. Correlation of Tract metrics with age and behavior. Final tractograms of LC projections were generated for all brains in the study and DTI and relaxometry values within these tracts were evaluated for their correlation with age and behavioral metrics. Promising significant correlations were found with FA but not MWF in this tract and secondary analysis is ongoing to determine the appropriate interpretation of these findings.
   - This work will be prepared as a manuscript for submission within a year once results are final.
4. Grant submission
   - R21 submission related to diffusion MRI in a rat model of AD was submitted although not successful. This will be the basis for a resubmission or part of a larger R01 proposal described below.
   - Upon publication of the two manuscripts described in 2,3 above, we will organize a full R01 proposal submission that includes the Bonnet macaque brains and focuses on the radiologic pathologic correspondence of age-related changes in microstructure during normal aging and with AD.
5. Additional progress toward long-term outcomes. The 2023-2024 project period produced final results in both research areas – microstructural MRI markers and LC tract changes with age. These serve the long-term goals of defining new MRI markers and should contribute to impactful publication of the research as a basis for future funding.

# ARIZONA ALZHEIMER'S CONSORTIUM
# 2023-2024 Scientific Progress Report

**Language Therapy Paired with Noninvasive Neuromodulation to Enhance Functional Language Skills in Logopenic variant of Alzheimer's Disease.** Aneta Kielar, PhD, Pelagie Beeson, PhD, CCC-SLP, Steven Rapcsak, MD, Mark Borgstrom, PhD. University of Arizona; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

## Specific Aims:

**Specific Aim 1:** To evaluate therapeutic value of phonological treatment paired with transcranial direct current stimulation (tDCS) on language performance in individuals with logopenic variant of primary progressive aphasia (lvPPA).
**Specific Aim 2.** To examine changes in neural function in response to treatment with active tDCS versus sham using measures of brain activation and functional connectivity.

## Background and Significance:

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that uses weak electric currents (1-2 mA) applied to the scalp to modulate brain responsiveness by temporarily altering neuronal resting membrane potentials[20–22]. TDCS can be combined with behavioral intervention to modulate neuronal excitability in task-relevant brain regions and thus optimize treatment effects. In lvPPA we are fighting against progressive decline as brain regions that support language undergo slow atrophy. The progressive nature of PPA provides an opportunity for tDCS combined with behavioral therapy to counteract the degeneration by promoting activation in vulnerable brain regions that remain functional and structurally preserved. Strategically placed neuromodulation has potential therapeutic value for individuals with lvPPA (and AD) to augment behavioral interventions that are designed to restore/preserve functionality. The results of this project will provide critical data needed to develop robust intervention in PPA combining speech-language therapy with tDCS that could be translated to clinical settings.

## Preliminary Data, Experimental Design and Methods:

**Preliminary Data.** Our pilot case series research demonstrated improved phonological ability that was greater after phonological intervention combined with active tDCS: phonological composite score increased from 45% to 70%, effect size = 0.93) compared to sham condition (62% increased to 67%, effect size = 0.13). Of particular interest was the significant improvement in reading and writing abilities. These generalization effects were larger when treatment was paired with active tDCS (61% → 81%, effect size = 0.87) versus sham (79% → 87%, effect size = 0.43).

**Experimental Designs and Methods. Participants** will be individuals diagnosed with lvPPA (~40-80 years old), randomized to receive active tDCS+language treatment or sham tDCS+language treatment in a cross-over design. **Phonological treatment paired with tDCS** will be 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 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. **Pre-post tDCS assessments and imaging.** To assess direct treatment effects, generalization and maintenance, participants will complete 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). Individual changes in neural function

and network connectivity in response to treatment will be examined with task-related and resting-state fMRI at each follow-up time point (Aim 2).

**Proposed One-Year and Long-Term Outcomes:**

**Year 1**: Over the first 2 months we will recruit and screen participants. During the next 10 months we will administer treatment protocol, follow-up assessments, and prepare publication. These findings 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.

**Year End Progress Summary:**

During the award period (July 2023 to June 2024) we enrolled 6 more participants with PPA increasing our sample size to n = 16 individuals who completed the full trial. Retention has been high, and the placebo-controlled trial is intended to continue until early 2026. Our results indicate that tDCS-first and sham-first groups both 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 an approach that targets phonological deficits in logopenic and nonfluent PPA. Specifically, we found that improved phonological skills resulted in better functional communication ability (text-level writing) relevant to everyday life. The analysis of neuroimaging data is ongoing. The case data from this study has been published in *Frontiers in Human Neuroscience* and another paper with group results is under review. Our group presented study results at two conferences and two invited symposia. This data also served as basis for student honors theses, independent research projects (4 student projects), and PhD dissertations *(K.V. Nickels: graduated in Summer 2023; F. Jebahi: graduation expected Spring 2025*). In the next stage we plan to collect genetic and blood-based biomarkers of AD that may influence response to the intervention. For this aspect of the study, we are collaborating with Arizona Clinical Core Laboratory and the UAHS Biorepository.

# ARIZONA ALZHEIMER'S CONSORTIUM
# 2023-2024 Scientific Progress Report

**Characterization of the Neuroinflammation in the 5xFAD Model for the Development of an Alzheimer's PK/PD Model.** Kathleen Rodgers, PhD. University of Arizona; Arizona Alzheimer's Consortium.

## Specific Aims:

Our lab focuses on the development of therapies for neurodegenerative disorders including Alzheimer's disease. In these efforts, it is crucial to have short duration *in vivo* models that allow the correlation of pharmacokinetics (PK) with pharmacodynamics (PD) to assess the relative efficacy of related compounds. Unfortunately, only a few studies have attempted to characterize neuroinflammation in young, prodromal 5xFAD mice and those have either used potentially suboptimal readouts (mRNA)[1] or expensive/time consuming imaging readouts (PET) both of which are not ideal for the rapid assessment of efficacy.[2] To address this issue, in this proposal, we are seeking to use facile and robust methods to characterize the onset and progression of inflammatory cytokines (by ELISA) and microglial polarization (by flow cytometry) in the 5xFAD mouse model to identify the optimal timepoint for testing neuroinflammation targeting therapies.

## Background and Significance:

Despite tremendous efforts, the development of new therapeutics for Alzheimer's disease (AD) suffers from the highest failure rates of any disease state.[3] AD is a devastating, progressive neurodegenerative disease that affects over 5.5 million Americans. AD is the 6$^{th}$ leading cause of death in the US and is the most common cause of dementia, making it one of the greatest therapeutic needs of the 21$^{st}$ century. While the brains of AD patients present with two pathological hallmarks, β-amyloid (Aβ) plaques and tau-containing neurofibrillary tangles (NFTs), the development of anti-Aβ and anti-tau antibodies as well as beta-secretase 1 inhibitors have been unsuccessful in the amelioration of AD-related cognitive decline. As a result, the identification of novel therapies for novel therapeutic targets for AD is desperately needed.

In addition to Aβ deposits and NFTs, neuroinflammation is a major hallmark of AD. Chronic, unresolved inflammation emerges during the prodromal phase of AD alongside amyloid pathology, mild cognitive impairment, and metabolic dysfunction.[4–9] Acute inflammation is crucial for protecting the brain by scavenging and clearing infectious agents, toxic proteins (Aβ), and damaged neurons. However, chronic neuroinflammation in AD leads to elevated levels of pro-inflammatory cytokines, oxidative stress, and microglial activation which ultimately results in neuronal death, neurodegeneration, and, ultimately, cognitive decline.

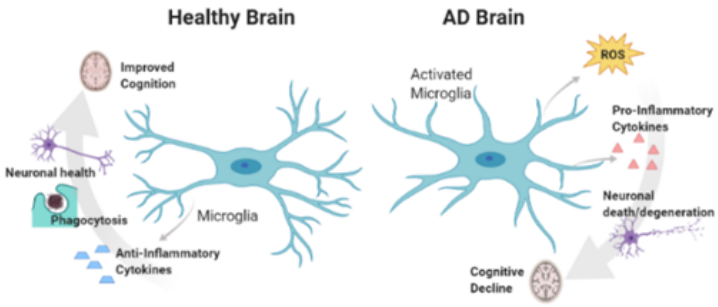


**Figure 1.** Role of neuroinflammation, microglial activation, and cytokines in the healthy and AD brain.

As a result, there is great interest in developing therapies targeting neuroinflammation to stop the decline or, ideally, reverse the cognitive decline in patients suffering from AD.

## Preliminary Data, Experimental Design and Methods:

We have extensive experience phenotyping microglial polarization by flow cytometry. In addition,

we routinely assess the effects of novel AD therapies on cognitive function in older 5xFAD mice. Unfortunately, these studies usually required aged 5xFAD mice and multiple months of treatment. As a result, we are excited to explore the potential of a shorter-term model to pre-screen compounds for the longer-term studies.

**Proposed One-Year and Long-Term Outcomes:**

The one-year goal of this work is to characterize the on-set and progression of neuroinflammation in the 5xFAD mouse model of AD. These efforts will set the stage for two, long-term outcomes. First, we will publish and present at relevant scientific conferences the details of our characterization the 5xFAD mouse model to empower other researchers developing neuroinflammation-targeting therapies with an optimized PK/PD model for assessing the efficacy of their therapies. Second, we will utilize this 5xFAD PK/PD model to assess the efficacy of our novel programs targeting neuroinflammation as treatments for AD. This data will enable us to advance these programs towards the clinic via NIH and/or DoD funding and industry and investor support.

**Year End Progress Summary:**

The objective of this study is to characterize peripheral and neuroinflammation utilizing this model. This characterization helps to determine the time frame in which therapeutics should be tested. Male and female 5xFAD mice were used in this experiment and 5 weeks, 2 months, 5 months, and 7 months of age. The tissues collected from each mouse included the brain, meninges, blood, and spleen. The right brain, meninges, and isolated white blood cells underwent cell dissociation to be stained for flow cytometry. Results showed an increase of inflammatory responses between the two-month and five-months age groups, indicating that this model does not provide a short term model for neuro-inflammation. Neuroinflammatory changes seen between two and five months of age included microglial activation (MHCII+ or CD14+) and of cross-talk between microglia (Interleukin 3+ microglia) and astrocytes (% of cells producing IL-3) via Interleukin-3. Activation of astrocytes appeared to occur prior to 5 weeks of age based upon GFAP+ astrocytes and comparison to mice much older without these mutations (ongoing studies are being conducted in the same strain of mice without the 5xFAD mutations at the same time points to confirm. No sex differences were seen in neuroinflammation.

Endothelial dysregulation was also seen between two months and 5 months of age in these mice as measured by expression of P selectin, ICAM and VCAM. Sex differences were observed in the expression of ICAM by endothelial cells at 2 months of age.

Peripheral inflammation was also assessed. Neutrophils and inflammatory monocytes increased between 5 weeks and 7 months of age. The effects were most pronounce on the migratory monocytes (those that are prepared to enter tissue. These data suggest that the peripheral immune system and blood brain barrier are affected in this model and contribute to the later increase in neuro-inflammation.

**ARIZONA ALZHEIMER'S CONSORTIUM**
**2023-2024 Scientific Progress Report**

**Psychosocial Stress and Diurnal Cortisol Profiles: Examining Biological Pathways of Cognitive Health Disparities Among Older Adult Latinos and Non-Hispanic Whites** Lee Ryan, PhD, Siobhan Hoscheidt, PhD, Matt Huentelman, PhD, John Altin, PhD, Lesley Guarena-Espinosa. University of Arizona; Tranlational Genomics Research Institute; Arizona Alzheimer's Consortium.

**Specific Aims:**

*Aim 1:* To compare diurnal cortisol profiles and psychosocial stressors in Latinos and Whites. Based on prior literature, we expect Latinos to have a lower wake cortisol level, lower cortisol peak, steeper drop after the peak, and overall flatter slope than Whites. Compared to Whites, Latinos are also expected to have overall worse scores on psychosocial stress measures.

*Aim 2*: To characterize the associations between psychosocial stressors and diurnal cortisol profiles among Latinos and non-Hispanic Whites. We predict that increased psychosocial stress will be associated with more flattened diurnal cortisol slopes across both racial/ethnic groups.

*Aim 3:* To assess the impact of psychosocial stressors (acculturative, perceived, chronic, traumatic events, childhood adversity, perceived discrimination) in cognitive outcomes by racial/ethnic group. We hypothesize that compared to Latinos, there will be a stronger association between psychosocial stressors and cognitive outcomes in Whites.

**Background and Significance:**

Hispanics/Latinos/Latinx, hereafter Latinos, are the largest racial/ethnic minority group in the US, comprising 19% of the population 60 years of age and older (US Census, 2021). While Latinos are a heterogenous group of diverse origins and heritages, Latinos of Mexican origin/heritage comprise 62% of all US Latinos (US Census, 2020). The US-Mexico bordering state of Arizona has a population that includes 32% Latinos (US Census, 2022), primarily of Mexican origin/heritage, providing a unique opportunity to investigate ADRD risk factors in this demographic group. While Latinos are known to live longer (Ruiz, Steffen & Smith, 2013), they are also at greater risk of ADRD when compared to non-Hispanic Whites, hereafter Whites (Alzheimer's Association, 2023). Latinos are at greater risk of health outcomes associated with greater risk for dementia, including CVD (de Bruijn & Ikram, 2014; Lamar et al., 2019), type 2 diabetes (Haan et al., 2003), and prolonged stress (Brown, Mitchell & Ailshire, 2020). These biological and psychosocial stressors pose a threat to cognitive aging in Latinos living in the US.

The hypothalamic-pituitary-adrenocortical (HPA) axis, a vital biological stress response system, is responsible for producing cortisol. A glucocorticoid hormone, cortisol is responsive to psychosocial, acute and chronic stress and plays an important role in cognitive functioning (Lupien et al., 2009). The hippocampi and prefrontal cortex have been found to have high concentrations of glucocorticoid receptors (Lupien & Lepage, 2001), making these areas particularly sensitive to cortisol changes due to HPA axis dysregulation. The hippocampus and prefrontal cortex are implicated in memory and executive functions domains of cognition. As such, cortisol dysregulation may provide important insight into the effects of psychosocial stress on cognitive outcomes and health conditions also associated with risk of cognitive decline.

Stress-associated elevated and dysregulated levels of cortisol have been linked with deleterious health outcomes including diabetes, cardiovascular disease, and Alzheimer's Disease and Related Dementias (ADRD) (Martocchia et al., 2015). Among a community-based sample of

racial/ethnic minority adults (mean age=58, 26% Latino), increases in psychosocial stress were associated with flatter cortisol slopes (DeSantis et al., 2015), which have been associated with poorer health outcomes such as diabetes and CVD (Rosmond & Bjorntorp, 2000; Matthews, Schwartz, Cohen, & Seeman, 2006). Similarly, a recent study in Mexican Americans found an inverse relationship between total daily cortisol levels and global cognitive function (Stebbins et al., 2021). While Stebbins and colleagues (2021) suggest that cortisol may impact cognition, it is unclear how cortisol patterns may influence global and domain-specific cognitive outcomes. Other studies suggest that flatter diurnal cortisol slopes may be implicated in exposure to trauma, stressful life events and interpersonal stress (Gunnar & Vasquez, 2001; Yehuda, Golier, & Kaufman, 2005; Ranjit, Young & Kaplan, 2005). As Latinos may be exposed to a myriad of stressors, it is important to understand the nuances of how psychosocial stressors may influence cortisol patterns and in turn, may influence cognitive performance and risk for ADRD.

**Preliminary Data, Experimental Design and Methods:**

A preliminary study, conducted by graduate student Lesley Guarena-Espinosa examined emotional health and its association with neurocognition in Hispanic and White individuals with HIV. Participants included 107 Hispanic and 216 Whites. Emotional health and cognition was assessed via the National Institute of Health Toolbox (NIHTB). Only in Whites, worse negative affect (fear affect, perceived stress, and sadness) was associated with worse cognition. In both groups, worse social satisfaction (emotional support, friendship, and perceived rejection) was linked with worse cognition. Results indicated that adverse emotional health is common among PWH, with subgroups of Hispanics showing relative strengths in some domains. Aspects of emotional health differentially relate to neurocognition.

**Participants** will be recruited via community outreach activities including community talks in Hispanic-oriented churches, community centers, health fairs, and via social media paid advertisements using culturally appropriate materials (i.e., flyers and messages). These efforts will be led by a Latina graduate student, Ms. Lesley Guarena-Espinosa, fluent in both English and Spanish and of Mexican American bicultural background. Building trust and race/ethnicity-concordant researchers facilitate research participation in underrepresented groups (Gilmore-Bykovskyi et al., 2019).

*Enrollment criteria*. 30 Latino and 30 White participants will be (1) age 50 to 75, (2) identify as Latino or non-Hispanic White, and (3) be comfortable with completing assessments in English. *Measures:* To compare Latino-White disparities via the National Institute of Aging's Health Disparities Research Framework (Hill, Pérez-Stable, Anderson & Bernard, 2015), we will obtain stress questionnaires, salivary cortisol collection, and neuropsychological testing.

**Questionnaires** will assess psychosocial stressors in Latinos and Whites will include perceived stress (Cohen et al., 1983), chronic stress (domains: personal health, familial health, financial strain, work stress, housing problems, relationship stress, caregiving stress; Bromberger & Matthews, 1996), traumatic events (Norris, 1990), childhood adverse events (Meinck et al., 2017), and perceived discrimination (Brandolo et al., 2005). Culturally relevant stressors and other factors to be assessed in Latinos will include familism (Steidel & Contreras, 2003), acculturation (Marin et al., 1987), and Hispanic ethnicity related stress (domains: occupational/economic, parental, marital, immigration, and cultural/family stressors; Cervantes et al., 2016).

**Salivary cortisol** samples will be collected at four time points, beginning at awakening, which is optimal for characterizing diurnal cortisol patterns (Adam et al., 2017). Saliva will be collected using specimen collection swabs provided to participants.

**Cold-pressor stress task** will be administered in the laboratory to assess stress reactivity and recovery. This method is effective for assessing HPA-axis function/dysfunction. Salivary cortisol will be taken at 6 timepoints to optimally characterize how "intact" the HPA-axis is (i.e., slope of recovery to baseline). Salivary cortisol will be frozen at -80C and assayed using ELISA.

**Neuropsychological testing** will be obtained via MindCrowd Expanded (www.mindcrowd.org) which assesses memory, executive functions, visual spatial, processing speed. The web-based format of the cognitive battery will aid in Latino completion as location and time are reported barriers to Latino research participation (Gilmore-Bykovskyi et al. 2019).

**Potential covariates** for analyses will be obtained including sex, education, socioeconomic status, depressive and anxiety symptoms, sleep, coffee intake, substance and alcohol use will be ascertained via self-reports. Additional data will be obtained from participants in PAN who wear a Garmin smartwatch for seven days/nights and keep an activity/sleep diary over the same period.

**Proposed One-Year and Long-Term Outcomes:**

The proposed study can be completed within the year and the results submitted for conference presentations and publication. Results of the present study will be shared in recruitment sites (churches, community centers) to continue engagement with the Latino community and provide a direct benefit of this research. Based on results of the study, pilot data will be leveraged to submit an NIH F31 or R21 grant proposal that will further elucidate potential stress-mediated mechanisms in health disparities of ADRD in Latinos.

**Year End Progress Summary:**

Data has been collected for 45 participants, including 30 non-Hispanic White (NHW) individuals and 14 Hispanic/Latino participants, with several others awaiting scheduling in July. To support recruitment, we held multiple recruitment activities in the Hispanic/Latino community of Tucson such as educational talks and attendance at local events. These community partnerships have resulted in an increase in study enrollment and will be invaluable as we continue to expand our studies of race/ethnicity groups. To enroll the remaining 16 Hispanic/Latino participants, we have created media advertisements for a local Hispanic radio station. These announcements will be ongoing for the next two months, beginning in July. We anticipate completing enrollment for the entire study by the end of August.

Preliminary analyses have been conducted with data collected thus far. Results indicated that the Hispanic/Latino group have higher levels of depressive symptoms ($p<.05$), while levels of stress, adverse childhood events, vigilance, and perceived discrimination are similar across both race/ethnic groups).

The salivary cortisol samples will be analyzed once data has been collected for all 60 participants. These measures will allow us to assess the relationship between objectively measured effects of stress such as stress reactivity, recovery, and HPA-axis function, with self-reported measures of stress as well as cognitive functioning. Best practice is to analyze the samples with ELISA in a single batch. In the meantime, samples have been cataloged and frozen in our biorepository at -80C.

**Future plans.** Collection of diurnal cortisol, in-visit cortisol saliva samples, and cognitive data are ongoing and should be completed by late August. Once all 60 participants have complete data, we will continue analyses to determine how salivary cortisol levels are associated with questionnaire and cognitive measures. We plan to submit results to be presented at the International Neuropsychological Society annual meeting in fall 2025 and may lead to an extramural grant application on this topic in spring 2026.

# ARIZONA ALZHEIMER'S CONSORTIUM
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**The Role of Deoxysphingolipids in Alzheimer's Disease.** Justin Snider, PhD, Anita Koshy, PhD. School of Nutritional Sciences and Wellness, University of Arizona; Arizona Alzheimer's Consortium.

## Specific Aims:

**Aim 1.** To determine the metabolic dynamics of novel DSL and cSL generation in AD affected neurons.

**Aim 2.** Test the hypothesis that increased SR activity shifts SL metabolism from cSL to the neurotoxic DSL metabolites in AD neurons

## Background and Significance:

Over 6 million Americans over 65 have Alzheimer's disease (AD), and this number is expected to double by 2060. AD involves systemic and localized CNS inflammation, leading to neuronal defects. The exact mechanisms by which amyloid beta (Aβ) plaques cause this pathology are unclear. This proposal utilizes lipidomic techniques to study the accumulation of 1-deoxysphingolipids (DSLs) in AD and how serine racemase (SR) regulates DSL levels. DSLs are neurotoxic and cannot be metabolized into more complex sphingolipids, leading to their accumulation. Increased SR activity and D-serine levels in AD exacerbate DSL production. The study will link altered D-serine metabolism to lipid dysfunction in AD, offering potential therapeutic insights. Understanding the impact of DSLs on AD pathology is crucial for developing new treatments.

## Preliminary Data, Experimental Design and Methods:

Preliminary Data: Our unbiased lipidomics approach identified 1-deoxysphinganine (dSA) as the most significantly elevated lipid in brain tissues from AD patients carrying the APOE3/3 allele as compared to age matched controls. Our lab next generated a targeted liquid chromatography mass spectrometry (LC/MS/MS) method to analyze DSLs and DMSLs. Our preliminary analysis revealed significant increases in multiple downstream DSLs, including C18 deoxy-dihydroceramide and deoxy-ceramide in APOE3/3 AD patients. Accumulation of DSLs has been observed in HSN and been shown to alter neurite outgrowth, similar to some pathologies that occur in AD progression.

## Experimental Design and Methods:

Aim 1. Metabolic flux will be assessed using isotopically labeled amino acids. Growth media for mouse neuron selection/maintenance will be dialyzed to deplete amino acids, then reconstituted with all except the amino acid of interest, which will be added as an isotopically labeled substitute. After Aβ treatment, labeled media will be added to neurons, and lipids will be harvested at specific time points. Total amino acid content and D serine ratio will be measured via LC/MS. Custom R-code will identify label incorporation in untargeted lipidomics by mass difference at the same retention time.

Aim 2. Cultured mouse neurons will be genetically modified via neuron-specific "Fuse-it-siRNA" kits to knockdown SR, SPT subunit 2, and ssSPTb, using non-targeting siRNA as a control. Knockdown efficiency will be confirmed by RT-PCR and western blotting. Post-transfection, cells will be treated with Aβ and analyzed through lipidomics, RT-PCR, and western blotting. SR inhibition effects will be studied using malonic acid and 2,2-dichloromalonate, with pretreatment

12 hours before Aβ exposure. SR activity and D serine ratios will be measured via LC/MS, and morphological changes in neurons will be monitored. Data processing will follow Aim 1 protocols.

**Proposed One-Year and Long-Term Outcomes:**

**Timeline and Plan for Submission of Competitive Grant Application**

The first 6 months of grant funding will focus on generating data from the experiments in this proposal. These data will be used for the submission of an R03 in February of 2024. The R03, a small research grant, will provide for additional personnel and research costs. The R03 will focus on generating this model in human derived IPSCs with a larger focus on manipulating SR to control the neuron and astrocyte D/L serine axis. The data produced by this grant will also be utilized in a collaborative publication between Dr. Koshy and I that will aid in our R01 application leveraging the PIs "Early Stage and New Investigator" status (after submission of R03). The lipid flux data produced in Aim 1a will also be utilized to support the submission of a Maximizing Investigators' Research Award – NIGMS grant (R35 MIRA) in 2024. This grant will focus on utilizing lipid flux to give context to currently accepted techniques that only provide a "snapshot" of lipid metabolism under experimental conditions. It will leverage the PI's lipidomic expertise to drive AD and cancer research in his lab.

**Year End Progress Summary:**

The opportunities provided by this grant laid a strong foundation for AD research in my laboratory. Over the past year we have had many exciting discoveries and learned the techniques to achieve success in this field. Initially all experiments in this proposal were planned to using neurons only, though upon literature review we realized a neuron astrocyte coculture (referred to neuronal cultures for the rest of the progress report) would be more amenable to the SR signaling mechanism we were trying to recapitulate. Setting up this system and optimizing protocols was a large undertaking, but thanks to the training by our collaborator on this grant (Dr. Anita Koshy) we were able to achieve this. Next, it was important to developed a quantitative pipeline to achieve a physiologically relevant ratio of neurons to astrocytes (2:1 to 3:1), through growing embryo derived cultures in B12 only 5 days and adding Ara-C till day 13 we were able to achieve a 2:1 ratio. Finally, the pipeline is finished by importing images into AutoNeuriteJ, an ImageJ plugin, to assess neurite morphology. For lipid and mRNA collection a similar pipeline is used in larger dishes. Setting up this pipeline was a large time and financial investment that required almost 4 months of optimization.

As funds were not distributed at the UA until September 2023, we did not begin actual experiments for Aim 1 until January 2024, once setting up our culture model was complete. Though in this time we have achieved some remarkable data, including:

1) We have demonstrated that DSLs are 2.3 fold increased in neuronal cultures treated with Aβ 1-42 (Aim 1a).
2) We **hypothesized** a shift in SPT substrate specificity from l-serine (canonical sphingolipid substrate (cSL)) to alanine (DSL substrate) upon addition of exogenous d-serine. We **observed** inhibition of cSL with chronic (24h) d-serine addition and a slight increase in DSL accumulation. Increasing levels of d-serine while maintaining constant concentrations of l-serine yielded a corresponding linear decrease in cSLs and modest linear increase in DSLs. As DSLs are extremely slow (if at all) to be degraded, these neurotoxic lipids should begin to accumulate over time with elevated d-serine generation in AD brain. This data indicated that d-serine may not alter substrate specificity, but in fact only inhibits the generation of cSLs and allows for normal production of neurotoxic DSLs. (Aim1b and 2a).

3) We are still optimizing labeling of SLs with isotopically labeled amino acid substrates (as well as accurately altering the amino acid composition of the media, hence the l-serine composition in aim1b remaining the same in this report). We have been able to achieve limited incorporation of serine isotope into *de novo* SLs. Further optimization includes switching from a dialysis of the media strategy to altering the media to MEM one hour prior to treatment with deuterated substrate. The initial data with label incorporation in will be utilized in an upcoming NIH MIRA grant. (Aim 1b and 2b)
4) We have only just begun to attempt transfection and knockdown of proteins in the neuronal cultures, thus far, we have not been successful and maintaining viable cultures post transfection. (Aim 2b)

This grant is currently acknowledged in 2 manuscripts: “Lipidomic Profiling of Frontal Cortex Reveals Dysregulated Fatty Acid Metabolism and Lipid Droplet Formation in Alzheimer’s Disease” that will be submitted to the Journal of Alzheimer's Disease in September of 2024 and the main manuscript being produced via the pilot and preliminary data.

Another goal of this pilot proposal was to acquire preliminary data for larger grant submissions. The investigator/collaborator submitted an R03 in June 2024 to “NIH- NIA-PAR-23-179: Small Research Grant Program for the Next Generation of Researchers in AD/ADRD Research” to Chronic Dysfunction and Integrative Neurodegeneration Study Section (CDIN) based on the data obtained over the last year utilizing neuronal cultures. Through a collaboration formed at the annual meeting AZ AD Consortium Retreat an internal grant was produced at the University of Arizona to look at exosome lipidomes and the transport of lipids between astrocytes and neurons. This pilot grant (AZADC) shifted from a focus on eventually modeling in IPSC to utilizing the neuronal cultures/techniques developed from this pilot. Also, the initial experiments were planned using C57BL/6 mice with Aβ 1-42 treatments, but upon discussing models with researchers at the retreat, we established the 5XFAD would be sufficient to establish the Aβ phenotype we believe will demonstrate DSL accumulation. Since the retreat we have been able to start a colony of the 5XFAD mice that were provided by another AZADC member. The fact that we now have the cell model, techniques, and mice in place significantly strengthens my upcoming proposals. The R03 will be followed with a grant entitled “Investigating the Influence of Sphingolipid Compartmentalization on Dynamic Cellular Signaling” being submitted to NIGMS for a Maximizing Investigators' Research Award (R35 MIRA) in October 2024. Lipid labeling work performed on this pilot grant produced data that is being used as an aim in the MIRA to better understand astrocyte and neuron cross talk.

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**Continued Quantification of Amyloid Beta Levels in Alzheimer's Disease Patients Using FLOWER.** Judith Su, PhD, Gene Alexander, PhD, Thomas Beach, MD, PhD. University of Arizona; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

**Specific Aim:**

The specific aim of this project is to continue to quantify amyloid-beta 42 levels in cerebral spinal fluid and serum from cadaver samples provided by the Brain Body Donation Program. This will be done using an ultra-sensitive optical sensing technique known as FLOWER which we have developed in our lab.

**Background and Significance:**

We have developed a technique known as FLOWER (frequency locked optical whispering evanescent resonator) that can detect low concentrations of molecules down to the single molecule limit without requiring the use of labels such as fluorescent or radioactive tags.[1–3] We are currently evaluating the ability of FLOWER to test for the Alzheimer's disease (AD) biomarkers amyloid beta and tau in both cerebrospinal fluid (CSF) and serum/plasma. There are potential benefits for applying FLOWER to both types of samples. For CSF, FLOWER offers greater sensitivity that could be easier to reproduce across labs than ELISA, which is the current gold standard. Furthermore, because of its particularly high sensitivity, FLOWER offers the potential to detect Alzheimer's disease biomarkers in serum and/or plasma, which can be more easily collected from participants with lower risk than the collection of CSF. This is especially conducive for repeated measurements for longitudinal studies. The serum/plasma detection can be directly assessed against the CSF markers to help validate the measures with established markers that reflect deposition in the brain. The objective of this one-year pilot project is to obtain the necessary preliminary data that demonstrates the feasibility of our approach and will form the basis for an R01 proposal, as well as for publications to further support this research plan. In a previous pilot project funded by the Arizona Alzheimer's Consortium, we focused on detecting the AD proteins amyloid beta and tau using FLOWER. This is related to an R03 (PI: Su; R03AG055020) we were awarded.

**Preliminary Data**:

To validate the feasibility of our technique in real sample analysis, clinical serum samples were analyzed to quantify pTau217 levels for AD diagnosis. It was expected that samples from healthy individuals would exhibit minimal or no wavelength shift during measurement, whereas significant wavelength shift intensities would be observed for AD patients due to reports of three-fold higher levels of tau proteins in their blood compared to healthy individuals. Initially, seven patients (labeled P1 to P7), whose clinical diagnoses were disclosed prior to analysis, were assessed. Patients P1 through P5 exhibited no increase in wavelength shift compared to the buffer, while positive wavelength shift responses were detected for P6 and P7. The estimated pTau217 levels present in the samples of P6 and P7 were ~1.3 pM and ~2.1 pM, respectively. Clinical reports revealed that the detection assay accurately identified five negative patients (i.e., P1 through P5) and one positive patient (P7). A correlation of the experimental results with clinical information indicated that no substantial increase in wavelength shifts was observed for P1 through P5 owing to their minimal reported tau tangle scores (ranging from 2 to 5), β-amyloid plaque scores (i.e., 0 or 3.5 in the case of P4) and plaque densities (zero for P1, P2, P3, and P5 or sparse for P4). In

the case of P7, higher tangle and plaque scores with moderate plaque density were reported, which boosted accurate detection using the WGM microtoroids. However, despite P6 being a healthy subject, clinical information disclosed a relatively high tangle and plaque scores, as well as moderate plaque density compared to the other healthy subjects, potentially impacting diagnosis accuracy and resulting in a false positive outcome. Nonetheless, the high diagnostic accuracy achieved indicates the promising potential of the developed platform for real sample applications.

Having confirmed the assay's ability to discriminate between healthy individuals and AD patients, a blind screening was further conducted on 33 patients using the established detection protocol. Two distinct groups, labeled as negative and positive, were discernable based on the estimated pTau217 concentrations in the individual serum samples. Concentrations ranged from 0.01 to 0.54 pM for the negative-labeled group and from 0.71 to 2.17 pM for the positive-labeled group. Given this notable concentration disparity, 23 samples were categorized as AD-negative (healthy individuals) while 10 were identified as AD-positive. Among the 33 patient samples, clinical information revealed that a total of 21 samples were accurately diagnosed (i.e., true positive or true negative) while 12 samples were misdiagnosed (i.e., false positive or false negative), as summarized in Figure 5a. The outcome indicated an overall prediction accuracy of ~64%. To comprehensively evaluate the diagnostic performance, a receiver operating characteristic (ROC) curve, illustrating the trade-off between sensitivity (true positive rate, TPR) and specificity (true negative rate, TNR) across various threshold values of the diagnostic test, was constructed based on the results obtained. The ROC curve revealed a TPR of 0.5, indicating that half of the patients with AD were accurately identified by the detection platform. Meanwhile, the area under the curve (AUC) value, which quantifies the overall performance of the diagnostic test, was calculated to be 0.85. Although a TPR of 0.5 suggests the potential for enhancing specificity, the relatively high AUC value of 0.85 demonstrates promising diagnostic capability, highlighting the potential usefulness of the assay in identifying individuals with AD.

**Experimental Designs and Methods:**

**FLOWER Set-up**. Optical fiber (Thorlabs SM600, Newton, NJ) was first tapered using hydrogen flame and a custom fiber-pulling stage (Newport, CA, USA). Light from a tunable laser (New Focus TLB-6712, Newport, CA, USA) was coupled into the fiber, and its transmission was gauged using an auto-balanced photodetector (Nirvana 2007, Newport, CA, USA). A polarization controller adjusts the laser's polarization and a 50:50 beam splitter splits light into the signal and reference arms of the auto-balanced photodetector. To enable frequency modulation, a dither signal is applied to the piezoelectric transducer within the tunable laser. Light from the WGM resonator enters the photodetector, capable of reducing laser intensity noise by 55 – 70 dB. The error signal, derived from the product of the dither signal and receiver output signal over time, reflects the difference between the laser wavelength and the WGM resonance wavelength. Utilizing a proportional-integral-derivative (PID) controller, the laser wavelength is regulated. By processing the error signal, the PID controller adjusts the laser controller feedback to minimize the error signal, ensuring the laser wavelength aligns with the WGM resonance wavelength. The microtoroid resonance frequency shift is measured with a Toptica Digilock 110. The photodetector's output connects to the Digilock, which sends an analog voltage output to both the tunable laser's frequency modulation input and a data acquisition card (DAQ) (PCI-4461, National Instruments). The Digilock generates an error signal by modulating the laser's frequency with a 2 kHz sine wave and compensates for any frequency shift by adjusting the voltage signals to the

laser and the DAQ card. Consequently, real-time shifts in WGM resonance, indicating particle binding, are tracked by monitoring the laser wavelength through the PID controller output.

**Fabrication of microtoroids**. Microtoroid structures were fabricated according to previously described protocol. In brief, a 2 μm thick layer of SiO2 was thermally grown on a silicon (Si) wafer and employed for the fabrication of microtoroids. Microdisks (150 μm diameter) and a wide support wall (350 μm) were patterned on the SiO2 surface with Microposit S1813 photoresist after exposing UV light through a photomask of opaque arrays on the photoresist array. Buffered oxide etchant (BOE) 6:1 was used to etch the exposed SiO2 down to the Si substrate, followed by a resist stripping with acetone and isopropanol. A XeF2 dry chemical etcher (Xactix e2, Orbotech, Yavne, Israel) was used to etch the exposed Si substrate after a dehydration bake at 130°C. The microtoroid structures (disks) and support wall were then reflowed using a $CO_2$ ($\lambda_0$ = 10.5 μm) laser before use.

**Microtoroid functionalization.** Microtoroids were functionalized by first immersing reflowed chips in APTES (dissolved in chloroform) solution for 15 min. The chips were carefully washed with EtOH and incubated in 100 mM succinic anhydride (dissolved in DMF) solution for 8 h under rotation. The microtoroids were subsequently incubated in EDC and sulfo-NHS mixture solution (100 mM; dissolved in MES buffer) for 15 min. Phosphor-tau polyclonal antibody as capture antibodies were immobilized by incubating chips in 10 μg/mL (except stated otherwise) antibody solution for 2 h under rotation. Chips were rinsed with 100 mM ethanolamine to remove non-specific binding and incubated in pTau217 standard solutions (2 h) or human serum samples (6 h, except stated otherwise) prior to measurements.

**pTau217 measurements.** Following surface functionalization, the microtoroid chips were secured within a 3D-printed fluidic chamber (internal volume approximately 120 μl) using a double-sided tape. A glass cover slip was positioned atop the fluidic chamber to contain the fluid. Fluid samples (i.e., pTau217 buffer and/or purified tau monoclonal solution as detection antibody) were introduced into the chamber via a syringe rack and electric rotary valve system (ASP-ERV-O1.2-16, Aurora Pro Scientific). The microtoroid was evanescently coupled with the tapered optical fiber using a 3-axis micrometer stage and a 3-axis piezo nanopositioning stage (P-611.3 NanoCube, PI, MA). Subsequently, the analyte sample was introduced into the fluidic chamber containing the microtoroid chip via a peristaltic pump operating at a flow rate of 10 μL/s; the fluidic chamber has an approximate volume capacity of 100 μL. Upon sample injection, resonant wavelength responses (binding events) were tracked in real-time by FLOWER as detailed previously. Here, the laser frequency was locked to the resonance frequency of the microtoroid using the Digilock frequency locking system. As molecules bind to the microtoroid surface and subsequently change the toroid's resonant frequency, the amount of voltage the feedback controller applies to the tunable laser to stay locked to the resonance wavelength of the microtoroid is recorded. This allowed molecule binding to be monitored in real-time.

**Proposed One-Year and Long-Term Outcomes:**

Our proposed one year outcome is to extend this study to patients whose blood was drawn < 18 months prior to death. In the long term, we would like to a direct sample comparison with SIMOA and extend our study to mild cognitive impairment patients.

**Year End Progress Summary:**

We used FLOWER to detect pTau217 in serum from cadavers. The overall prediction accuracy was approximately 64%, supported by a receiver operating characteristic curve (ROC) with an area under the curve (AUC) value of 0.85. Despite some misdiagnoses, the validation shows the platform's ability to differentiate between non-AD and AD patients based on pTau217 levels in clinical serum samples. Further statistical analysis reveals a positive correlation between pTau217 concentrations and amyloid plaques as well as a significant correlation between pTau217 and tau tangles, further validating the utility of FLOWER in AD diagnosis. The high diagnostic accuracy demonstrates the potential utilization of the developed platform for real sample applications, highlighting its promise for clinical use in disease diagnosis.

**ARIZONA ALZHEIMER'S CONSORTIUM**
**2023-2024 Scientific Progress Report**

**MRI and Multispectral Two-Photon microscopy of blood-brain barrier integrity in AD mice.**
Theodore Trouard, PhD, Elizabeth Hutchinson, PhD, Paulo Pires, PhD. University of Arizona; Arizona Alzheimer's Consortium.

**Specific Aims:**

1. **Utilize intravital multispectral Two-Photon microscopy to determine the cerebrovascular distribution of microbubbles injected into WT and AD mice.** Understanding the temporal and spatial distribution of microbubbles in the brain vasculature of mice being treated with FUS for BBB opening is critical to developing this technique for treatment of ADRDs. Using novel multispectral 2-Photon experiments, we will characterize the distribution of microbubbles in the mouse brain in vivo. We will also develop rapid line-scanning two-photon microscopy to determine the size distribution of microbubbles in-vivo.

2. **Utilize FUS and contrast-enhanced MRI to determine the time course of BBB permeability and AQP-4 channel regulation throughout the entire brains of WT and AD mice.** We *hypothesize* that immediately after FUS application, the rate of extravasation of fluid from the vasculature into the brain, $K^{trans}$, will be significantly increased in the sonicated region, and will return to baseline within 24 hours. We also *hypothesize* that 24 hours post-FUS, astrocyte activation and AQP-4 channel upregulation will be significantly increased in the sonicated region and will return to baseline within 48 hours.

**Background and Significance:**

Alzheimer's Disease (AD) is the most prevalent neurodegenerative disease in the United States, with an estimated 5.8 million Americans over the age of 65 affected [Alzheimer's & Dementia 2020]. Despite the prevalence and severity of AD, there is currently no cure. It is well known that a major obstacle hindering therapeutic research for the central nervous system (CNS) is the blood-brain barrier (BBB), a layer of endothelial cells, basement membrane, and astrocytic endfeet that creates a barrier between capillaries and parenchyma [Aryal 2014]. Focused ultrasound (FUS) has been introduced as a novel method of transiently opening the BBB for drug delivery and therapy in neurodegenerative disease [Hynynen 2001]. A growing body of literature has demonstrated the safety and efficacy of acute treatment using FUS [Liu 2021, Downs 2015, Jordao 2010, Lipsman 2018], however, researchers have found that multiple treatments of FUS can have a greater therapeutic effect than single FUS applications [Liu 2021]. There is an urgent need for a better understanding of mechanisms of BBB opening and the long term effects of multiple FUS treatments on BBB integrity [Todd, 2020].

Previous experiments have shown that astrocytes and AQP-4 channels are increased significantly 24 hours' post-sonication, and return to baseline after 48 hours [Han 2021], and that $K^{trans}$, a volume transfer constant, increases immediately after sonication and returns to baseline within 24 hours [Chai 2014, McMahon 2020]. ***These studies indicate that FUS causes changes to water and solute transport acutely, but these parameters have not been examined in mouse models of AD or after multiple treatments of FUS***. The rationale behind this application is that understanding these acute and longitudinal effects of FUS-mediated BBB disruption in a mouse model for AD and will add to the body of literature evaluating the utility of FUS to treat ADRDs.

The Trouard lab at the University of Arizona has developed the capability for conducting FUS-mediated BBB opening in mice and the Hutchinson lab at the University of Arizona has developed the capability of multispectral, intravital 2-photon microscopy in living mice. These capabilities will be combined in the current project and will produce novel data on the mechanisms of BBB opening and the effects of BBB opening on fluid transport in the brain.

**Preliminary Data:**

**The ability to temporarily open the BBB in mice has been demonstrated.** Two-photon intravital mouse brain images of fluorescent dextrans delivered to the vasculature and interstitial spaces has been carried out.

**Year End Progress Summary:**

MRI, ultrasound and 2-photon in vivo microscopy has been completed on WT and transgenic 5xFAD mice. Results are being analyzed and preliminary findings have been presented at state and international meetings.

# ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Research MRI Peripherals and Electronics Support.** Theodore Trouard, PhD, Ali Bilgin, PhD, Nan-kuei Chen, PhD, Maria Altbach, PhD, Gene Alexander, PhD, Ying-hui Chou, PhD, Arne Ekstrom, PhD, Lee Ryan, PhD, Wei Zhou, MD, Craig Weinkauf, MD, PhD, Scott Kilgore, PhD, Aneta Kielar, PhD. Biomedical Engineering, University of Arizona; Arizona Alzheimer's Consortium.

**Specific Aims:**

This grant is to provide peripherals and electronics to support the new 3T MRI instrument that is being purchased through a $2M NIH High-End Instrumentation (HEI) grant awarded to the University of Arizona. The peripherals and electronics are needed to enable AAC researchers to transition projects to the new instrument. Some MRI time and technologist time are required for the installation and evaluation of the peripherals and to carry out evaluation of the new system.

**Year End Progress Summary:**

This AAC funding has been used to purchase the following equipment:

- Current Designs button controller kit
- Tektronix 200 MHz Oscilloscope
- Three desktop computers to run peripheral MRI equipment
- Cambridge Research MediGlasses vision correction lenses
- Console large screen TV/monitor
- Comply MRI earbud tips
- Console audio equipment
- FOMRI microphone
- Cambridge Research MRI-compatible screen
- Bracco MRI contrast injectors

This peripheral equipment greatly enhances the TBIR's ability to support neuro-imaging-based research projects on the new 3T Cima.X MRI system.

While the purchasing of this peripheral equipment was done according to our intended schedule, the arrival of the Cima.X MRI system has been significantly delayed. The system was expected to receive FDA approval and start shipping in October of 2023 but that didn't happen until January 2024. However, more impactful was that in August of 2023 we discovered a major construction mistake created by miscommunication between Siemens and the University of Arizona. As a result, we needed to move the equipment room for the Cima.X to a new space. Planning and funding this new work took a significant amount of time and our new construction timeline shows a Cima.X delivery in early December 2024.

# ARIZONA ALZHEIMER'S CONSORTIUM
## 2023-2024 Scientific Progress Report

**Metabolic Mechanisms of Reactive Astrogliosis in Alzheimer's Disease.** Fei Yin, PhD, Francesca Vitali, PhD, Haiwei Gu, PhD. University of Arizona; Arizona State University; Arizona Alzheimer's Consortium.

**Specific Aims:**

1) Define the metabolic response of astrocytes to proinflammatory stimuli.
2) Compare the metabolic signatures of normal vs. Alzheimer's disease (AD) associated astrocytes upon proinflammatory activation.
3) Determine the metabolic mechanism(s) underlying altered inflammatory response in AD associated astrocytes.

**Background and Significance:**

Astrocytes represent the most abundant cell population in mammalian brain, and they regulate essential processes including synaptic development and transmission, blood flow, and inflammatory response by interacting with other cell types in the brain. Intercellularly, astrocytes play a critical role in metabolically supporting neighboring neurons by 1) producing lactate as neuronal bioenergetic substrates, and 2) clearing neuronal lipid waste via an ApoE-dependent process. On the other hand, astrocytes are critically involved in neuroinflammation by receiving and propagating proinflammatory signals initiated by microglia or from the periphery. These signals transform astrocytes from their homeostatic state towards diverse reactive phenotypes (termed reactive astrocyte). Chronic and sustained astrocyte reactivity (reactive astrogliosis) is a hallmark of Alzheimer's brains, and these transformed cells are defined as disease-associated astrocytes (DAAs).

Our recent work has revealed both cell autonomous and non-autonomous mechanisms by which astrocytic metabolic deficits trigger reactive astrogliosis, neuroinflammation, synaptic loss, and cognitive impairment. Both DAA genes and AD-related genes were substantially activated upon astrocytic mitochondrial dysfunction. Further, we discovered that both amyloidosis and the ApoE4 allele, key drivers of AD, metabolically program astrocytes and promotes their proinflammatory transformations (partially supported by AAC Projects 2019-2020, 2021-2022 and 2022-2023). These findings point towards a mechanistic role of astrocytic metabolic phenotype in determining their response to reactive stimuli.

Research proposed here will test our hypothesis that the metabolic capacity of astrocytes determines their susceptibility to proinflammatory activation promoting AD progression and can therefore be therapeutically targeted to facilitate the resolution of neuroinflammation. Outcomes from this study will generate initial evidence for future validation in animal models and human cells and postmortem tissues. If our hypothesis is tested true, then restoring the metabolic fitness of DAAs could be an effective therapeutic strategy to alleviate AD-associated reactive astrogliosis and chronic neuroinflammation.

**Preliminary Data, Experimental Design and Methods:**

Our hypothesis is based upon our prior work and supported by our preliminary data. Primary astrocytes isolated from wildtype (WT) mice were treated with proinflammatory cytokines (IL-1α, TNF, and C1q) for 24 hours. Compared to those treated with vehicle, cytokine-treated astrocytes were highly reactive and exhibited significantly reprogrammed metabolic phenotype characterized by elevated glycolysis, increased of phospholipid hydrolysis, suppressed de novo fatty acid synthesis, and accumulation of neutral lipids in lipid droplets (LDs). Phenotype of these astrocytes

recapitulates that of astrocytes with dysfunction mitochondria. Together, our data support the critical role of metabolic reprogramming in disease-associated transformation of astrocytes.

Proposed experiments were performed with primary astrocytes isolated from WT or AD mouse brains as described previously. Primary astrocytes were treated with vehicle or cytokine cocktails including IL-1α (3 ng/ml), TNF (30 ng/ml) and C1q (400 ng/ml) for 24 hours. After treatment, astrocytic metabolic preference and metabolic capacity in terms of glucose and fatty acid oxidation will be determined by the Seahorse XF Analyzer as described previously. In addition, metabolites or metabolic markers involved in both glucose and lipid metabolism will be assessed. Further, pharmacological modulators (agonists or antagonists) will be used to activate or block candidate metabolic pathways or enzymes to determine whether they could restore the altered inflammatory response in AD associated astrocytes.

**Proposed One-Year and Long-Term Outcomes:**

Upon completion of the proposed studies, we expect to generate initial evidence for a metabolic-inflammatory cascade implicated in reactive astrogliosis that can be therapeutically targeted to restore astrocyte homeostatic phenotype. Outcomes of the proposed studies will be used to seek external funding from the National Institute on Aging or private agencies to validate the mechanism and determine the translational potential using AD animal models in vivo and in human cells and/or postmortem tissues.

**Year End Progress Summary:**

1. Lipid metabolic reprograming mediates proinflammatory stimuli-induced astrocytes reactivity

Consistent with our preliminary data showing increased LDs accumulation in cytokine-treated astrocytes, IL-1α, TNF, and C1q treatment resulted in elevated levels of lipid classes including free FAs (FFA) and triacylglycerol (TAG). IL-1α, TNF, and C1q treatment not only reprogrammed lipid metabolic hemostasis, but also substantially increased the phosphorylation of NFκB (p-NFκB) and the acetylation of STAT3 (acetyl-STAT3$^{Lys685}$), as well as the secretion of inflammation mediator, prostaglandin E2 (PGE2), indicative of higher reactivity. In parallel with reactive astrogliosis, cytokine-treated astrocytes showed lower maximal respiration and ATP production, which was accompanied by higher levels of lactate and upregulation of key glycolytic enzymes, including hexokinase 2 (HK2) and 6-phosphofructo-2-kinase/ fructose-2,6-bisphosphatase-3 (PFKFB3).

To determine the mechanism by which IL-1α, TNF, and C1q treatment induce astrocyte reactivity, we tested whether fatty acid β-oxidation (FAO) is involved in the process. Intriguingly, while blocking long-chain FA transport into the mitochondria with etomoxir (CPT1 inhibitor) had no effect on p-NFκB and acetyl-STAT3$^{Lys685}$ levels. Given that decreased FAO and acetyl-CoA production are not sufficient to trigger astrocyte reactivity under cytokine stimulation, we speculated that elevated cytosolic FFAs may play a role. Intriguingly, inhibition of adipose triglyceride lipase (ATGL, the enzyme that breaks down TAG in LDs) substantially increased LD volume in cytokine-treated astrocytes, it also abrogated the increase in PGE2 and lactate level. Furthermore, activation of SCD1 (stearoyl-CoA desaturase-1, the enzyme that produces unsaturated fatty acyl moieties for fluent storage into LDs) exaggerated cytokine-induced LD accumulation as expected, and it partially rescued cytokine triggered glycolysis activation. These results suggest that reducing cytosolic FFAs accumulation by storing them into LDs could mitigate cytokine treatment-triggered astrocytes reactivity.

2. ApoE4 compromises astrocytic response to cytokine stimulation

To compare the metabolic responses of ApoE3 and ApoE4 astrocytes to proinflammatory stimulation, primary astrocytes isolated from ApoE3 and ApoE4 mice was treated with proinflammatory stimuli, and their metabolic phenotype was determined. Intriguingly, while TNFα+IL1α+C1q treatment significantly enhanced the synthesis and release of proinflammatory PGE2 in ApoE3 astrocytes, such an effect was less prominent in ApoE4 astrocytes. Consistently, mRNA levels of proinflammatory cytokines IL1α and IL6 were less increased in ApoE4 astrocytes.

We then investigated whether the differential inflammatory response of ApoE3 and ApoE4 astrocytes can be attributed to their distinct lipid metabolic phenotype. Consistent with their inflammatory response, ApoE3 astrocytes responded to TNFα+IL1α+C1q treatment by accumulating substantially more LDs. However, despite a higher LD load at the basal condition than ApoE3 astrocytes, ApoE4 astrocytes responded to cytokine stimuli by reducing intracellular LDs, which suggests that the storage of lipids in LDs may already reach its capacity at the basal condition for ApoE4 astrocytes. Collectively, these data suggest that ApoE4 astrocytes have a compromised response to cytokine stimulation, which could be mechanistically linked to altered lipid metabolism and LD formation.

Partially based on findings generated from this and previous AAC-funded projects, an NIH R01 grant was awarded in April 2024 to determine whether and how altered astrocytic FA degradation modifies AD onset and progression and whether it can be therapeutically targeted (**RF1 AG079157; 2024-2029; PI: Yin**).

# ARIZONA ALZHEIMER'S CONSORTIUM
# 2023-2024 Scientific Progress Report

**Cognitive Effects of Carotid Disease and Carotid Intervention.** Wei Zhou, MD, Ted Trouard, PhD, Ying-hui Chou, PhD, Chiu-Hsieh Hsu, PhD, Gloria Guzman, Jose Elchieveri. University of Arizona; Surgical Services, Southern Arizona VA Health Care System (SAVAHCS); Washington University; Arizona Alzheimer's Consortium.

**Specific Aims:**

1) Determine the impact of baseline CBF on the characteristics of carotid intervention-related SBIs and cognitive changes.
2) Relate resting-state fMRI (rs-fMRI) changes to cognitive changes following carotid interventions.

**Background and Significance:**

Decreased CBF and frequent microembolization are two important etiologies of cognitive dysfunction in patients with asymptomatic carotid stenosis. Carotid revascularization is an effective strategy for stroke prevention. Although there is an overall cognitive benefit of carotid intervention[1,2], up to 30% of patients experience procedure-related cognitive deterioration despite an absence of neurologic complication[3].

There is a high incidence of procedure-related microembolization that lead to SBIs (20-80%) despite of an absence of clinical symptoms. We and others have shown that patients with procedure-related SBIs have poor cognitive performance comparing to those without, suggesting that SBIs contribute to post-intervention cognitive decline. We believe that poor clearance of emboli in regions of lower perfusion leads to increased incidence of SBIs.

Our **central hypothesis** is that impaired baseline CBF increases the risk of intervention-related SBIs and leads to cognitive deterioration. By understanding the dynamic interaction between CBF, the characteristics of SBIs, and their cognitive effects, we will have a better understanding of cognitive impairment and vascular dementia.

**Preliminary Data:**

**1. Cognitive changes following carotid interventions**: 170 consecutive patients with severe extracranial carotid bifurcation disease underwent revascularization procedures and received neuropsychometric testing pre-intervention, and at 1-, 6-, and 12-month postoperatively. Episodic memory was evaluated using Rey Auditory Verbal Learning test (RAVLT) with parallel forms. Executive function was evaluated with multiple cognitive tests. Age and education-adjusted postoperative scores at the individual postop time point were compared with the preoperative scores using paired T test and McNemar's test. We observed significant improvement in multiple executive function measures at 1, 6, and 12 months following carotid intervention. We also observed significantly improvement in episodic memory 1 and 6 months following carotid intervention. However, 30% of patients experienced significant decline despite of an improvement in the overall cohort. (*Annals of Surgery 2022; 276(3):539-544; PMCID: PMC9387545*).

**2. Related CBF to cognitive function**. Among the patients mentioned in study 1, 58 patients also received baseline MRI with arterial spin labelling (ASL) sequence. CBF maps were quantified using PCASL. We found that baseline ASL CBF is significantly correlated with baseline executive function measured by Trial Making Test (P=0.03) after adjusting for age, gender and BMI.

**Experimental Design and Methods:**
To explore the interaction between CBF and SBI, we will recruit 10 subjects who undergo carotid intervention from SAVAHCS. Subject will receive pre and postop brain MRI including DWI sequence to detect procedure-related SBIs. The subjects will also receive preop, 1 and 6 months postop neuropsychological tests focusing on the memory measure, as well as MRI ASL sequence at the same time to calculate whole brain CBF (tCBF). We plan to perform exploratory analysis to examine the impact of baseline tCBF on SBIs and cognitive changes in Aim1. We will correlate tCBF changes with changes in memory function.

In aim 2, we plan to analyze resting state function MRI (rs-fMRI) because rs-fMRI provides objective assessments of brain hemodynamic and functional changes. We will correlate baseline rs-fMRI measures with preop and postop cognitive function. We will also determine whether changes in tCBF correlate to rs-fMRI changes

**Proposed One-Year and Long-Term Outcomes:**
We expect to generate useful preliminary information on CBF changes and correlations between CBF and SBIs at one year. we will also expect to identify obstacle in resting state fMRI measures. These preliminary data is critical for our NIH grant application in next 18 months.

**Year End Progress Summary:**
***Prospective patient recruiting***: we submitted documents for VA central IRB, which is required per VA research office. At this time, the VA central IRB is still pending. Meanwhile, we have decided to recruit patients from Banner University of Medical Center. 3 subjects have completed MRI evaluations. We also performed subgroup analysis on 170 subjects in our data base who have underwent neurocognitive evaluation.

***Cognitive effects of carotid revascularization in octogenarians***: The sample was divided into 2 groups based on age: Octogenarian (≥80 years), and Non-Octogenarian (< 80 years old). Postoperative cognitive scores were compared to baseline within each sub-cohort. A total of 23 subjects (13%) were octogenarians, and 147(87%) were younger than 80 years. When compared to the baseline, octogenarians exhibited a trend of decline in verbal memory z-scores at 1 month (-1.09 vs. -0.93, p=0.247), and 6 months postop (-1.04 vs. -0.62, p=0.152). No postop score improvement was noted on measures of executive function in seniors older than 80 years. The study suggests that despite that carotid intervention has a positive impact on cognitive functions, seniors older than 80 years did not experience the positive cognitive benefit associated with carotid intervention. *Surgery 2023; 174(4): 1078-1082. PMCID: PMC10528540*

***Carotid Revascularization is Associated with Improved Mood in Patients with Advanced Carotid Disease***: Baseline depression (GDS>9) was observed in 49(31%) subjects, whereas 108(69%) patients were not depressed (GDS≤9). The average pre-operative GDS score was 15.42 ± 4.40(14.2-16.7) and 4.28 ±2.9(3.7-4.8) in the depressed and non-depressed groups, respectively. We observed a significant improvement in GDS scores within the depressed group at 1-month (p=0.002), 6-months (p=0.027), and 1-year (p<0.001) post-intervention compared to preop, whereas the non-depressed group had similar post-op GDS scores at all time points compared to baseline. Significant improvement in measures of executive function was seen in non-depressed patients at all three timepoints whereas depressed patients showed an improvement at 1-year follow-up. *Ann Surg. 2024, PMID: 38258598*

**Barriers to Antiplatelet and Statin Adherence Following Major Vascular Intervention:** A total of 101 subjects underwent major vascular intervention were examined. Approximately 90% of patients were discharged with aspirin, 32% with a P2Y12 antagonist, and 96% with a statin. Consistent adherence at 12 months was documented in 76% of patients on aspirin, 81% on P2Y12 antagonism therapy, and 73% on statins. New adverse drug reactions represented the most common barrier to achieving adherence (37%). Preoperative therapy with aspirin, P2Y12 antagonists, and statins were all independently predictive for postoperative adherence to the same regimen ($p<0.001$). Female gender was also associated with higher rates of adherence ($p<0.05$). *Annals of Vascular Surgery, 2024; (29): S0890-5096(24)00245-0. PMID: 38821476*

# ARIZONA ALZHEIMER'S CONSORTIUM
# 2023-2024 Scientific Progress Report

**Understanding the Role of Resistin in Vascular Dysfunction and Cognitive Impairment.**
Wei Zhou, MD, Paulo Pires, PhD, Mitchell Lazar, PhD. University of Arizona School of Medicine; University of Pennsylvania Perelman School of Medicine; Arizona Alzheimer's Consortium.

## Specific Aims:

1. Characterize human resistin-related arterial stiffness and advanced atherosclerosis in our newly developed murine models.
2. Explore the role of human resistin in cognitive impairment using experimental models.

## Background and Significance:

There is increasing evidence supporting the ability of the central nervous system to incite an inflammatory response to a variety of injuries including ischemia and trauma. Inflammation has been linked to cognitive decline and risk of dementia. Many studies, including ours, have associated postop inflammatory biomarkers to poor cognitive performance long-term.

Resistin is considered a link between diabetes and obesity in mice. Increasing clinical evidence associate human resistin with insulin resistance, obesity, arterial stiffness, and cardiovascular disease. High plasma resistin level is also associated with neuroinflammatory markers, early cognitive decline, and dementia in many population-based investigations. *In vitro* studies demonstrate resistin-induced macrophage proinflammatory transformation. To understanding the role of human resistin in cardiovascular disease and vascular dementia, we need to overcome the fact that human resistin and mouse resistin are significantly different.

Over the last two years, we have successfully bred ***Retn*$^{-/-}$** and ***Retn*$^{-/-}$*/BAC-hRetn*** (transgene) mice. The transgene mice lack murine resistin, but express human resistin on macrophages at the level similar to that in humans. We also recently developed two new murine models: ***Retn*$^{-/-}$*:Apoe*$^{-/-}$** and ***Retn*$^{-/-}$*/BAC-hRetn:Apoe*$^{-/-}$**. Both new models have no murine resistin and were cross-bred with *Apoe*$^{-/-}$, an atherogenic strain that displays impaired learning and memory functions. *Retn*$^{-/-}$*/BAC-hRetn:Apoe*$^{-/-}$ mice express human resistin in macrophages similar to in human. In this proposal, we will utilize these novel murine models to study the role of resistin in inflammation, arterial remodeling, and vascular dementia.

## Preliminary Data:

***Pressure myograph to evaluate vessel compliance*:** To prove feasibility of evaluating physiological response of human resistin, we conducted a preliminary study of arterial stiffness on 23-week old male and female *Retn*$^{-/-}$ and *Retn*$^{-/-}$*/BAC-hRetn* (transgene) mice that were fed with normal chow or high fat diet (HFD) for 4 weeks. Middle cerebral arteries (MCA) were then isolated and analyzed using pressure myograph. We observed that HFD alone increased arterial compliance of *Retn*$^{-/-}$ mice, but decreased compliance of transgene mice, suggesting that HFD increases arterial stiffness in the presence of human resistin.

***Tissue comparison of Apoe*$^{-/-}$ *and Retn*$^{-/-}$*/BAC-hRetn:Apoe*$^{-/-}$ *mice***: We observed advanced atherosclerotic plaques in older *Apoe*$^{-/-}$ and *Retn*$^{-/-}$*/BAC-hRetn:Apoe*$^{-/-}$ mice. Both strains have the presence of resistin with mouse resistin being in *Apoe*$^{-/-}$ mice and human resistin in *Retn*$^{-/-}$*/BAC-hRetn:Apoe*$^{-/-}$ mice. To differentiate the in vivo effect of mouse and human resistin, we examined the brachiocephalic arteries of 12-week old animals, we observed significant higher

vascular cell adhesion protein 1 (VCAM-1) expressions in *Retn$^{-/-}$/BAC-hRetn:Apoe$^{-/-}$* compared with *Apoe$^{-/-}$* mice (P=0.02), suggesting that human resistin play a more significant role in the genesis and progression of atherosclerosis than mouse resistin.

**Experimental Design and Methods:**

In this study, we will leverage our novel murine models. *Retn$^{-/-}$* mice will be compared to *Retn$^{-/-}$ /BAC-hRetn* mice to determine the role of human resistin. Retn$^{-/-}$:Apoe$^{-/-}$ mice will be compared to *Retn$^{-/-}$/BAC-hRetn:Apoe$^{-/-}$* mice to evaluate the impact of human resistin in mice with known atherosclerotic and cognitive risks. Mice will be fed with NC or HF diet to determine diet-related effects.

We will first characterize human resistin-related arterial stiffness and advanced atherosclerosis in our newly developed murine models using pressure myograph and immunohistochemical methods. Then we will test the spatial memory of our four novel strains using a T-maze model.

**Proposed One-Year and Long-Term Outcomes**:

At one year we expect to have preliminary data on the relationship between resistin and cognitive changes, we will expect to have a better understanding of the effects of human resistin on arterial compliance. Our long-term plan is to determine the impact of human resistin on vascular dementia and cognitive impairment using these novel genetically modified mice. We plan to submit a NIH application in the next 18 months.

**Year End Progress Summary:**

***Effects of human resistin on structure and biomechanical properties of MCA***: 26-28 weeks old *Retn$^{-/-}$* and *C57BL6 WT* mice were fed with normal chow or HFD with or without human resistin infusion (via osmopump) for 4 weeks. We found that absence of resistin increases wall thickness of females mice, but no effects on male mice. However. there was a decreased MCA compliance in both male and female *Retn$^{-/-}$* mice. Human resistin infusion mitigated structural remodeling in females, and biomechanical remodeling in males. When HFD was added to *Retn$^{-/-}$,* both male and female MCAs remodeled, and females also showed decreased compliance.

***Role of human resistin in advanced atherosclerosis***: To ensure that we have a true atherogenic model. We further analyzed the atherosclerotic plaques of a *Retn$^{-/-}$/BAC-hRetn:Apoe$^{-/-}$* mouse. The thoracic aorta and aortic arch were isolated from a 40-week-old animal fed with normal chow. We observed extensive advanced atherosclerotic plaque within the thoracic aorta, aortic arch, and its branches. Immunohistochemical analysis of the carotid artery showed large lipid droplets within the atherosclerotic plaques (Red: Lipid stained with Oil red-o) and abundant macrophage deposition with the atherosclerotic plaque as well (Green: Macrophage stained with Alexa 488 conjugated F4/80 antibody).

# UNIVERSITY OF ARIZONA
# COLLEGE OF MEDICINE – PHOENIX
# PROJECT PROGRESS REPORT

# ARIZONA ALZHEIMER'S CONSORTIUM
# 2023-2024 Scientific Progress Report

**Plasma Biomarker and Vascular Pathophysiology in Aging, Injury, and Disease.** Jonathan Lifshitz, PhD, Katherine R. Giordano, PhD, Callie A. Mahrer, MS, Kyli A. McQueen, Daniel R. Griffiths. University of Arizona College of Medicine – Phoenix; Phoenix VA Health Care System; Arizona Alzheimer's Consortium.

## Specific Aims:

1) To validate plasma biomarker presence in acute TBI clinical samples as they relate to clinical measures of injury severity and outcome; explore presence of TBI biomarker in clinical samples of neurodegenerative disease. *Hypothesis: The protein biomarker is detectable as a binary signal across multiple clinical variables and isolated as a unique entity.*
2) To extend funded work on cumulative brain injury by investigating pathophysiological mechanisms through surface coated nanoparticles and histopathology of cerebral vasculature. *Hypothesis: Cumulative experimental brain injury attracts monocyte-coated particles to regions of cerebrovascular compromise.*

## Background and Significance:

[1] Prior studies, partially supported by AAC and NIH funding, led the research team to a novel plasma biomarker for TBI in diffuse brain-injured rodents. The commercial antibody could be applied in a novel approach to stratify brain-injured from uninjured samples, with particular utility in the resolution of brain injury pathophysiology. Protocol refinement has allowed us to transition from commercial approaches to standard western blot for detection. A current working protocol exists for human blood samples, including serum and plasma. Evidence suggests that plasma provides a clear indicator of the results, but human samples more often involve serum analysis. The biomarker – under proprietary non-disclosure – is undetectable in commercial pooled plasma and serum samples from healthy control. Human serum samples have been procured from the Banner Sun Health Brain and Body Donation program to evaluate 4-6 samples per degenerative condition. Legal and collaborative agreements allowed the material transfer of banked human blood samples from a clinical trial treatment for TBI. The existing western blot protocols are sufficient to detect the biomarker of interest. Current gaps in knowledge relate to the specific antigen, the specificity of the antibody, the range of degenerative conditions responsive to this biomarker, and the utility added to existing blood based biomarkers.

[2] Our miniature microscope (miniscope) technology and chronic vascular pathology leading to dementia has focused our outcomes on the cerebrovasculature. Accumulating evidence suggests an acute disruption of the blood brain barrier, likely mediated by glial activation, and possibly sustained through more chronic periods of the disease process. Our collaborator Mark Wang (ASU) manufactures monocyte membrane-coated or platelet membrane-coated particles for eventual therapeutic delivery to inflamed tissue. We continue to explore the targeting of particles to areas of TBI-induced vascular pathology where the manufactured particles would bind. Feasibility trials have been attempted with coated and uncoated particles, with encouraging outcomes. Similarly, the vascular pathology that expresses antigens to attract coated particles must be identified histopathologically. Areas of antigen expression likely represent focal areas of cerebrovascular pathology.

**Preliminary Data, Experimental Design and Methods:**

[1] A plasma-based biomarker discriminated brain-injured from uninjured animals over time post-injury. Western blot protocols have been optimized for human serum and plasma samples. De-identified human samples from the Banner Sun Health Brain and Body Donation program were obtained to present healthy and aged/diseased conditions. Traditional western blots were run on agarose gels and identified the potential antigen of interest. New studies with brain injury samples are required to determine the specificity from aging and disease. To improve understanding of the antigen, mass spectrometry of the isolated western blot band is necessary, as well as validation of all commercial antibodies marketed against similar epitopes.

[2] Miniature microscopes visualize fluorescent compounds in the vasculature and cortex under a cranial window. During combinations of high-speed and time-lapse imaging, fluorescent compounds are administered to observe vascular morphology and function, with regard to dye-tracer permeability from the vasculature. Administration of closed-head injury with miniscope imaging demonstrated that vascular permeability was minimal, and encouraged more severe injury administration. Studies are needed to evaluate other fluorescent compounds in understanding the pathophysiology of TBI, particularly related to the vasculature.

**Proposed One-Year and Long-Term Outcomes:**

Mr. Griffiths is the primary technical lead on both aims. Dr. Giordano is responsible for the informatics analysis between the biomarker expression and the clinical data. Ms. Mahrer has particular interest in cerebrovasculature and will lead the spatial transcriptomics studies. Ms. McQueen has expertise in histopathology and will process and quantify tissue for cerebrovascular damage and particle accumulation, while training Ms. Mahrer. Mr. Tallent will manage the laboratory function and conduct western blots and histological staining, as needed.

Serum samples from Banner Sun Health have been received and the translation of protocols from plasma to serum and rodent to human are complete. Western blots and a quantification strategy should be complete by Q1 of the funding period for post-mortem samples. This milestone will prepare the study team to receive hundreds of TBI samples for processing and quantification. A set of positive biomarker samples will be pooled and processed by the Proteomics core facility in an attempt to isolate the antigen. Parallel studies will be conducted with multiple commercial antibodies purported to detect the same antigen. Successful results may support an invention disclosure.

The protocols to produce an array of coated particles are now standard practice in Dr. Wang's laboratory, as are the brain injury protocols in Dr. Lifshitz's laboratory. Studies can commence immediately upon funding to generate animals and tissue necessary for the assessment of TBI pathophysiology in the cerebrovasculature. If sufficient preliminary data are obtained, extramural funding will be sought. The hypotheses to be addressed consider the cellular mechanism and fundamental change in the cerebrovasculature in response to diffuse brain injury.

**Year End Progress Summary:**

[**1**] A pilot project from the Banner Sun Health Brain and Body Donation Program availed 24 blood samples for biomarker analysis. The samples permitted protocol refinement to compare biomarker performance in serum and plasma, where the results were expectedly different, and the biomarker remained viable to identify aging/disease conditions. The conclusions drawn are that post-mortem blood, due to the chronicity of disease and delayed acquisition are less clinically informative or clear. Therefore, no definitive biomarker signature was conclusive for any of the conditions.

Extracted western blot bands of interest were subjected to mass spectrometry. The results were inconclusive due to the current protocol not depleting abundant proteins. Therefore, c-reactive protein (CRP) was the principle identified molecule, which does not align with the primary epitope of the biomarker of interest. Alternate strategies are proposed, but none (e.g., protein arrays) will maintain the specificity of the commercial antibody. Similarly, none of the alternate antibody sources identified a binary band of interest similar to the original antibody. Therefore, work continues on systematic evaluation of clinical samples on hand from brain-injured subjects. [**2**] Our research team has advanced technical capability to build, modify, implant, and use miniscopes to visualize brain dynamics during behavior. Ongoing work has collected high-speed and time-lapse imaging of fluorescent dextrans (multiple molecular weights) and labeled glucose to evaluate cerebral blood flow and blood brain barrier permeability. Ongoing work this year refined analytical approaches to quantify results from video. The goal is to determine vascular from parenchymal fluorescent signal, which indicates extravasation across a selective versus permeable blood brain barrier. Work continues in the context of experimental TBI to understand the cerebrovascular compromise, while performing histological assessments of vascular damage. Work to date has been unable to localize nanoparticles to injured vasculature, primarily due to the inability to produce pathology within the visual field.


# 2023 – 2024

# Publications & Manuscripts

## 2023 Publications and Manuscripts

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# 2023 – 2024

# Current & Pending Grants

## 2023-2024 Current Grants

**Robert Bowser (PI)**
1OT2NS136939-01 09/25/2023 – 09/24/2024
NIH/NINDS $16,733,501
Access for All in ALS (ALL ALS) West Clinical Coordinating Center

**Robert Bowser (PI)**
PM Core 01/01/2021 – 12/31/2025
Target ALS $2,500,000
Tissue Banking Consortium

**Robert Bowser (PI)**
AL2020-61 04/01/2021 – 07/31/2024
Department of Defense/USAMRAA $881,302
Targeting CNS expression of chitinases as a novel therapy for ALS

**Robert Bowser (PI)**
Biofluids Core 01/01/2021 – 12/31/2025
Target ALS $6,536,680
ALS Longitudinal Biofluids and Clinical Data

**Robert Bowser (PI)**
BB-2022-C5-L2 12/01/2022 – 11/30/2024
Target ALS $260,000
Does the accumulation of disease-associated forms of TDP-43 in platelets parallel ALS pathophysiology in the nervous system?

**Robert Bowser (PI)**
CZI Diversity Program 12/14/2022 – 12/13/2024
Target ALS / Chan Zuckerburg Initiative $588,500
Expanding diversity, representation and recruitment

**Robert Bowser (Co-I)**
R61 NS119642-02 12/01/2021 – 11/30/2026
NIH/NINDS $3,830,563
Targeting CNS expression of chitinases as a novel therapy for ALS

**Robert Bowser (Co-PI)**
R01 NS091299-06 08/01/2022 – 07/31/2027
NIH/NINDS $3,200,000
Translation dysfunction in neurodegeneration

**Robert Bowser (mPI- Bakkar/Bowser)**
AL220164 07/01/2023 – 06/30/2025
Department of Defense/USAMRAA $707,134
Longitudinal neuroimaging and molecular biomarkers of cerebrovascular health in ALS

**Robert Bowser (mPI-Medina/ Bowser)**
AL220103 07/01/2023 – 06/30/2025
Department of Defense/USAMRAA $782,284
Retinoid-activating gene therapy for the treatment of amyotrophic lateral sclerosis

**Anna Burke (Sub-I)** 04/01/21-03/31/26
NIH/NIA R01AG073212 (Multi-PI) $2,500,000
Repurposing Siponimod for Alzheimer's Disease

**Anna Burke (Sub-I)**
R01 R01AG059008 (DeCourt/Sabbagh) 09/01/2020-05/31/2025
NIH NIA $1,197,348 Total
MCLENA-1: A Phase II Clinical Trial for the Assessment of Safety, Tolerability and Efficacy of Lenalidomide in Patients with Mild Cognitive Impairment Due to Alzheimer's Disease

**Anna Burke (Sub-I)**
Alzheimer's Drug Discovery Foundation (ADDF) 04/01/2022-03/31/2027
MCLENA-2: Assessment of Lenalidomide for Alzheimer's Disease $1,396,475 Total

**Anna Burke (Sub-I)** 09/15/19-08/31/24
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

**David Medina (PI)**
R21 R21NS116385 (Bowser Co-PI) 09/01/2021-06/31/2024
NIH NINDS $435,387 Total
Novel knock-in mouse models of ALS and myopathy-linked Matrin 3 mutations

**David Medina (PI)**
DOD AL2201013 07/01/2023-06/30/2025
Retinoid-activity gene therapy for the treatment of AML $782,284 Total

**David Medina (PI)**
AAC/BNF 07/01/23-06/30/2024
The role of Matrin 3 in dementia $114,000

**David Medina (PI)**
AAC/BNF 08/01/23-06/30/2023
Matrin 3 Mechanisms in Neurodegeneration $136,800

**Elliott Mufson, (Multi-PI)** 04/2023-03/2028
NIA RF1AG081286 $3,378,346 Total
Default mode network dysfunction in Down syndrome

**Elliot Mufson (Co-PI)** 09/30/2023-08/32/2026
US Department of Defense Award 13685123 $750,000 Total
Anti-inflammatory biologic (XPro1595) treatment for neurological outcomes following TBI

**Elliott Mufson (PI)** 09/01/1997-01/31/2026
NIA PO1AG014449 $11,980,125 Total
Neurobiology of Mild Cognitive Impairment in the Elderly

**Elliott Mufson (Multi-PI)** 03/31/2018–4/01/2024
NIA R01AG061566 $1,637,064 Total
Tau pathology in Down syndrome and Alzheimer's disease

**Sylvia Perez (Multi-PI)** 4/1/2023-3/31/2026
NIA RF1 AG081286 $1,844,755
Default mode network dysfunction in Down Syndrome

**Sylvia Perez (Co-Investigato**r) 09/01/1997-01/31/2025
NIA P01 AG14449 $1,151,647
Neurobiology of mild cognitive impairment in the elderly

**Marwan Sabbagh (PI)** 05/15/17-04/30/23
LBDA1811MS $13,500
Research Center of Excellence (RCOE) designation

**Marwan Sabbagh (PI)** 09/01/18-08/31/24
NIH/NIA R01AG059008 $1,198,348
A Phase II Clinical Trial for the Assessment of Safety, Tolerability, and Efficacy of Lenalidomide in Patients with Mild Cognitive Impairment Due to Alzheimer's Disease

**Marwan Sabbagh (PI)** 09/15/19-08/31/24
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)

**Marwan Sabbagh (Multi-PI)** 04/01/21-03/31/26
NIH/NIA R01AG073212 $2,500,000
Repurposing Siponimod for Alzheimer's Disease

**Marwan Sabbagh (PI)** 01/01/22-06/30/26
ADRC- 1P30AG072980-01 $530,221.50
Arizona Alzheimer's Disease Research Center

**Marwan Sabbagh (PI)** 09/15/22-07/31/27
ADNI-U19AG024904 not to exceed $1,200,000
Alzheimer's Disease neuroimaging initiative -4

**Marwan Sabbagh (PI)** 01/01/23-12/31/27
GC-2013717 $1,396,475
Assessment of Lenalidomide for Alzheimer's Disease

**Marwan Sabbagh (PI)** 07/01/23-06/30/24
23-500-377-30-03 $114,000
AAC/BNF
Barrow Neurological Institute, Phoenix

**Rita Sattler (PI)** 04/11/24-08/31/26
NIH/NINDS 3R01NS120331-03S1 (Diversity Supplement award) $155,884
The role of an aberrant synaptome in microglia-associated synaptic pruning in C9orf72 FTD

**Rita Sattler (PI)** 04/01/24-03/31/26
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)** 09/01/23-08/31/26
Muscular Dystrophy Association #1063968 $300,000
Role of astrocyte-microglia crosstalk in C9orf72-mediated cortical neurodegeneration

**Rita Sattler (Multi-PI)** 09/01/23-08/31/25
Skylight Charitable Trust $500,000
Interplay between C9orf72 ALS and neurotrophic viruses: Impact on viral and ALS disease pathogenesis.

**Rita Sattler (Co-PI)** 09/01/23-08/31/28
NIH/NINDS R01 NS091299-06A1 $3,215,000
RNA dysregulation in neurodegeneration.

**Rita Sattler (PI)** 07/01/23-06/30/24
Arizona Alzheimer's Consortium (AAC) $99,091
Generation of induced pluripotent stem cells (iPSC) from LBD patients and temporal characterization of iPSC-differentiated neurons

**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 (Co-PI)** 07/01/23-06/30/28
NIH/NINDS R01NS127108-01 $3,350,000
Genomic analysis of the Multiplex, Autozygous Populations in Cerebral Palsy (MAP CP) cohort: a focused approach to a complex disease.

**Rita Sattler (Multi-PI)** 08/01/22-7/31/25
NIH/NINDS R21 NS128550-01 (NCE) $427,960
Transcriptomic assessment of pathology in PD with dementia and dementia with lewy bodies using iPSC neurons and brain tissue of the same individual

**Rita Sattler (PI)** 09/22/22-08/31/25
NIH/NINDS R21 NS130492-01 (NCE) $345,567
Mechanisms of A-I RNA editing-mediated nuclear export of TDP-43

**Rita Sattler (PI)** 09/01/21-08/31/26
NIH/NINDS R01 NS120331-01A1 $4,073,311
Microglia contribution to disease pathogenesis in C9orf72 ALS/FTD.

**Rita Sattler (PI)** 04/01/21-03/31/24
Department of Defense AL200139 $664,780
Targeting Synapse Loss in ALS/FTD using spine regenerating compounds

**Rita Sattler (PI)** 12/01/21-03/31/24
NIH/NINDS R21 NS130492-01 (NCE) $415,637
Astrocyte regulation of cortical neurodegeneration in C9orf72 FTD/ALS

**Ashley Stokes (PI)** 01/01/2022 – 09/30/2026
NIH/NINDS R01 NS124575 (Stokes) $1,996,900 Total
Multi-scale functional connectivity in preclinical models of Parkinson's disease

**Ashley Stokes (PI)** 06/01/2022 – 05/31/2025
NIH/NINDS R21 NS125535 $421,958 Total
Investigating the role of cerebral perfusion in demyelination and repair in multiple sclerosis with MRI

**Ashley Stokes (PI)** 01/13/2023 – 01/12/2026
Arizona Biomedical Research Centre RFGA2022-010-26 $750,000 Total
Assessment of neurovascular factors implicated in mild cognitive impairment and Alzheimer's disease

**Ashley Stokes (MPI)** 07/01/2020 – 06/30/2027
NIH/NCI R01 CA213158 $50,000 Total
Establishing the validity of brain tumor perfusion imaging

**Ashley Stokes (MPI)** 04/01/2025 – 03/31/2027
NIH/NCI UG3/UH3 CA247606 $712,019 Total
Structural and Functional Imaging for Therapy Response Assessment in Brain Cancer

**Nadine Bakkar (Co-PI) / Ashley Stokes (Co-PI)** 07/01/2023 – 06/30/2025
Department of Defense, CDMRP $707,134 Total
Longitudinal Neuroimaging and Molecular Biomarkers of Cerebrovascular Health in ALS

**Ashley Stokes (Co-I)** 07/01/2018 – 06/30/2024
NIH/NIA P30 AG019610-20 (Reiman; Core PI: Alexander) $6,149,580 Total
ARIZONA ALZHEIMER'S DISEASE CORE CENTER (ADCC): Brain Imaging and Fluid Biomarkers (BI-FB) Core (Core G)

**Ashley Stokes (Co-I)** 12/01/2022 – 06/30/2026
U.S. Dept of Veterans Affairs I01RX002691-01A2 (Migrino) $1,200,000 Total
Mechanistic role of vascular dysfunction in TBI-mediated cognitive dysfunction

**Bryan Woodruff, PD/PI** 6/19/2024-6/30/2025
AAC2016A-11P3 $2,984,973
Normal and Pathological Aging Preclinical Alzheimer's Disease

**Bryan Woodruff, PD/PI** 09/2020 - 03/2026
AG069453 $1,435,336
APOE in the Predisposition to, Protection from and Prevention of Alzheimer's Disease

**Bryan Woodruff, Co-I** 7/1/2023-6/30/2024
NIH/1P30AG072980-01, Reiman $ --
Banner Health
Arizona Alzheimer's Disease Research (ADRC)

**Bryan Woodruff, Co-I** 12/2023 - 11/2028
1R01MH132746-01A1, Braden $ --
Arizona Board of Regents for and on behalf of Arizona State University
Subaward No.: ASUB00001619
The Aging Autistic Brain: Multi-modal imaging to predict accelerated memory

**Richard Caselli, Co-I** 03/2021 - 02/2024
R03 AG070486 (NIA) $ --
Machine learning to predict incident MCI using standard clinical measures

**Richard Caselli, Co-I** 09/2020 - 03/2026
AG069453 $ --
APOE in the Predisposition to, Protection from and Prevention of Alzheimer's Disease

**Richard Caselli, Co-I** 07/2021 - 06/2025
AAC2016A-11P3 $ --
Normal and Pathological Aging Preclinical Alzheimer's Disease

**Richard Caselli, Co-I** 09/2021 - 06/2026
NIH/1P30AG072980-01, Reiman $ --
Banner Health
Arizona Alzheimer's Disease Research (ADRC)

**Dona Locke, Co-I** 6/19/2024-6/30/2025
AAC2016A-11P3, Woodruff $65,530
Normal and Pathological Aging Preclinical Alzheimer's Disease

**Meredith Wicklund, PD/PI** 1/2/2023-1/1/2026
221AD305 ENVISION/BIOGEN #51 $664,975
Biogen MA, Inc.
22-007913/221AD305/A Phase 3b/4 Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Verify the Clinical Benefit of Aducanumab (BIIB037) I Participants with Alzheimer's Disease

**Meredith Wicklund, PI** 7/1/2023-6/30/2024
NIH/1P30AG072980-01, Reiman $202,629
Banner Health
Arizona Alzheimer's Disease Research (ADRC)

**Leslie Baxter, Co-I** 12/7/2023-11/30/2024
1R01MH132746-01A1, Braden $26,404
Arizona Board of Regents for and on behalf of Arizona State University
Subaward No.: ASUB00001619
The Aging Autistic Brain: Multi-modal imaging to predict accelerated memory

**Mary Ellen Koran, PI** 08/2022 - 08/2024
Clinical Scientist Fellowship (Funded by Alzheimer's Association)
Characterizing Cervical Lymphatics in Aging and Alzheimer's Disease

**Gina Dumkrieger, PD/PI** 7/1/2022-6/30/2024
American Brain Foundation/Foundation Award $150,000
ABF #2
Clinical Research Training Scholarship in Migraine

**Charles Adler, PD/PI** 7/1/2023-6/30/2025
State of Arizona/NCE $728,603
CTR056041-01-03
Submandibular gland needle core biopsy as a tissue biomarker the diagnosis of Parkinson's disease and the monitoring of disease progression

**Charles Adler, PI** 12/1/2021-11/30/2026
NIH/Award Number 5R01NS122226-03, Bishop $94,384
The Research Foundation for the State University of New York
Interrogating maladaptive serotonin Raphe-Striatal plasticity in L-DOPA-induced dyskinesia

**Charles Adler, PI** 9/15/2021-8/31/2025
National Institute on Aging Award # 5R01NS118669-03, Beach $281,716
Banner Health dba Banner Health Research Institute
Blinded Comparison of Different Alpha Synuclein Seeding Assays as Cutaneous Biomarkers of Lewy Body Dementias

**Charles Adler, PD/PI** 11/1/2022-12/31/2033
Michael J. Fox Foundation for Parkinson's Research $2,925,901
PPMI 060 MJFF-021407
The Parkinson's Progression Markers Initiative (PPMI)

**Shannon Chiu, PD/PI** 6/1/2022-5/31/2027
NIH/Award Number 1K23AG073525-01A1 $781,028
Title: Neurodegeneration and Neuronal Fluctuations in DLB and AD

**Oana Dumitrascu, PI** 07/01/2023- 06/30/2024
ADHS14-052688 (Developmental Award - AAC) $50,000
Retinal Imaging Application in Preclinical Alzheimer's Disease

**Oana Dumitrascu, Co-I** 07/01/2023- 06/30/2024
23MRFSCD1077177, Chong (American Heart Association) $100,000
Risk modeling of stroke and cardiovascular disease using machine-learning based prognostic models from longitudinal encounters of patients with migraine

**John Fryer, PD/PI** 8/1/2019-6/30/2024
NIH – Award 1RF1AG062110-01 $4,000,571
Microglial apoE in neuroinflammation and Alzheimer's Disease

**John Fryer, PD/PI** 8/15/2020-8/31/2024
NIH- FAIN: RF1AG062077 $4,037,235
Novel Genetic modifiers of C9orf72 and Tau toxicity

**John Fryer, PD/PI** 4/1/2020-3/31/2030
NINDS - NS84974-10P1 $614,015
Pathobiology of Neurodegeneration in C9ORF72 repeat expansion

**John Fryer, PD/PI** 9/20/2019-6/30/2025
NINDS – 5U54NS110435-05 $1,486,750
Synergistic Interaction of amyloid-beta and alpha-synuclein in Lewy body Dementia

**Zonghui Ding, PI** 05/01/2022-04/30/2024
ADHS14-052688 (Developmental Award - AAC) $100,000
Targeting APOE and CLU in Alzheimer's Disease with single-domain antibodies

**Layla Al-Nakkash (PI), Tom Broderick, Minsub Shim** 07/01/2023-06/30/2024
AZ Dept of Health Services-Arizona Alzheimer's Consortium $23,250 Total
Involvement of the brain-muscle axis in western diet induced Alzheimer's pathology

**Nancy Bae (PI), Mark Swanson (Co-I)** 07/01/2023-06/30/2024
AZ Dept of Health Services-Arizona Alzheimer's Consortium $117,500
Assessing the DNA binding properties of the human telomere protection protein RAP Total Project

**Tom Broderick (Co-PI)** 04/15/2021-05/31/2024
Phoenix VA Healthcare System $28,760 Total
Mechanistic Role of Vascular Dysfunction in TBI-mediated Cognitive Dysfunction

**Kimberly Bussey (Co-Investigator)** 08/01/2023-06/30/2027
1R25HG012330-01 $27,500 Total Project
NIH R25 (Subaward from Arizona State University)
Training in Genomics Research (TiGeR)

**Stephanie Christensen (Non-key Co-project Director)** 11/01/2023-10/31/2028
U.S. Department of Education Office of Special Education & Rehabilitative Services $1,274,578 Total Project
Translational Adapted Groups: Community Builds Capacity for School SLPs

**Tiffany Hughes (Co-I)** 08/28/2023-02/28/2025
5R37AG023651-18 $65,078 Total Project
NIH R37 (Subaward from University of Pittsburgh)
Mild Cognitive Impairment: A Prospective Community Study

**Elizabeth Hull (PI) & Kathryn Leyva (Co-I)** 07/01/2023-06/30/2024
AZ Dept of Health Services-Arizona Alzheimer's Consortium $30,000 Total Project
Elucidating a mechanistic link between progranulin and lysosomal function in Alzheimer Disease

**Elizabeth Hull (PI) & Kathryn Leyva (Co-I)** 07/01/2023-06/30/2024
AZ Dept of Health Services-Arizona Alzheimer's Consortium $15,000 Total Project
Progranulin Transport & Processing: Implications for Development of New Alzheimer's Therapies

**Garilyn Jentarra (Co-PI)** 08/09/2021-08/15/2023
7R21AG072561-02 $459,771 Total Project
NIH R21 (Subaward from Florida International University)
Targeting Whole Body Fatty Acid Metabolism in Alzheimer's Disease, with Special Interest in Lauric Acid

**Garilyn Jentarra (PI) & T. Bucky Jones (Co-PI)** 07/01/2023-06/30/2024
AZ Dept of Health Services-Arizona Alzheimer's Consortium $61,524 Total Project
Evaluation of Regional Differences in Bacterial DNA Presence in the Brain Tissue of Alzheimer's Disease Patients and Controls

**Ann Revill (PI)** 07/20/2020-06/30/2024
R15HL148870 $447,700 Total Project
NIH R15 REAP
Cholinergic Modulation of XII Motoneurons and XII Premotoneurons

**Minsub Shim (PI)** 12/01/2019-11/30/2023
R15CA246429 $450,000 Total Project
NIH R15 REAP
Cyclooxygenase-2 Signaling in Cell Senescence and its Role in Chemotherapy-induced Long-term Adverse Sequelae

**Minsub Shim (PI), Layla Al-Nakkash (Co-PI),** 07/01/2023-06/30/2024
**Tom Broderick (Co-PI)** $21,450 Total Project
AZ Dept of Health Services-Arizona Alzheimer's Consortium
Geroscience approach to Alzheimer's disease: mitigation of cellular senescence by intermittent fasting

**Mark Swanson (PI) & Nancy Bae (Co-I)** 07/01/2023-06/30/2024
AZ Dept of Health Services-Arizona Alzheimer's Consortium $21,276 Total Project
Determining the molecular mechanism of activation of γ-secretase by the telomere protein RAP1

**Volkmar Weissig (Co-PI)** 09/01/2022-08/31/2024
Arizona Biomedical Research Commission $49,602 Total Project
(Subaward from AZ Veterans Research and Education Foundation)
Validation & Development of Nanoliposomes for Neuroprotection in Stroke

**Emily Cope (PI)** 07/01/2023-06/30/2024
CTR040636 (Cope) $150,000 Total Project
Arizona Alzheimer's Consortium Alzheimer's /AZDHS
Arizona Statewide Alzheimer's Research

**Emily Cope (PI)** 09/01/2021-08/31/2024
NIH/NIA R21AG074203 (Cope) $418,000 Total Project
Development of in vivo quantitative stable isotope probing to quantify microbiome dynamics in Alzheimer's disease

**Emily Cope (Project PI)** 09/20/2022-05/31/2027
NIH/NIMHD 2U54MD012388-06 (Baldwin, J.) $1,817,500 Total Research
Southwest Health Equity Research Collaborative (SHERC) $27,669,552 Total Award

**Emily Cope (Pilot Project PI)** 09/01/2012-08/31/2024
NIH NCI 5U54CA143925 (Ingram) $240,000 Total Project
The Partnership for Native American Cancer Prevention
Pilot Project: Addressing health disparities in H. pylori infection in Native American populations.

**Emily Cope (Pilot Project Co-I)** 06/30/2024-07/01/2026
NIH/NIMHD 2U54MD012388-06 (Baldwin, J.) $100,000 Pilot Project
Southwest Health Equity Research Collaborative (SHERC)
Pilot Project: Diet quality, GI health, and the gut microbiome in rheumatoid arthritis (PPP PI: Yoder, M)

**Greg Caporaso (PI)** 07/01/2020-06/30/2025
NIH 1U24CA248454-01 (Caporaso) $3,798,959 Total Project
Advanced Development of Informatics Technologies for Cancer Research and Management

**Greg Caporaso (PI)** 09/01/2021-08/31/2024
2021-237226 (5022) (Caporaso) $399,300 Total Project
Chan-Zuckerberg Initiative/Silicon Valley Community Foundation
Engaging Native American Students in Scientific Computing w QIIME 2 (EOSS-D&I)

**Greg Caporaso (co-I)** 09/01/2019-08/31/2024
NIH/NCI 5U54CA143925 (Ingram) $302,400 Total Project
The Partnership for Native American Cancer Prevention

**Greg Caporaso (Co-I)** 01/2024 – 12/2024
U000483134 $14,603 Total Project
University of Utah / Cumming Foundation
Exploring the role of gut microbiota dysbiosis in primary sclerosing cholangitis

**Greg Caporaso (PI)** 09/2021 – 08/2024
2021-237226 (5022) $399,300 Total Project
Chan-Zuckerberg Initiative
Engaging Native American Students in Scientific Computing with QIIME 2

**Traustadóttir, PI** 06/2022-05/2025
NIH/NIA 1R15 AG074088-01 (PI:Traustadóttir) $448,752 Total Project
Treatment strategy to enhance Nrf2 signaling in older adults: combining acute exercise with the phytochemical sulforaphane.

**Traustadóttir, PI** 04/2024-06/2025
NAU TRIF (PI:Traustadóttir) $19,119 Total Project
Reducing basal redox stress to improve stress resilience in older adults.

**McCarthy, M; Cerino, E.; McCoy, M. (Co-PIs)** 07/01/2023-06/30/2024
Arizona Alzheimer's Consortium Alzheimer's /AZDHS $160,000 Total Project
Development of Tailored Technologies and Resources to Identify and Support Rural Caregiver-Receiver Dyads with Mild Cognitive Impairment Due to Alzheimer's Disease – Year 1

**McCarthy, M. (Consultant)** 01/01/22-12/31/27
R01NR020184 (Bakas) $3,876,661 Total Project
Telehealth Assessment and Skill-Building Intervention for Stroke Caregivers (TASK III)

**McCarthy, M (Co-I, Site PI)** 7/1/2024-6/30/2029
1 U1QHP53053-01-00 (Fain) $4,923,639 Total Project
HRSA Arizona Geriatrics Workforce Enhancement Program

**Cerino, E. (PI)** 07/01/2023-06/30/2025
Pilot Project Program, NIMHHD (U54MD012388; Baldwin) $100,000 Total Project
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
NIA U19AG051426 (Almeida) $3,992,718 Total Project
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 Total Project
Institutional Champion for NIH's All of Us Research Program.

**Cerino, E. (Co-I)** 07/01/2023-06/30/2025
Social Sciences and Humanities Research Council of Canada (Rush) $74,572 Total Project
Day-to-Day Influence of Climate Change Distress on Daily Well-Being and Climate Action Behaviors

**McCoy, M.C. (PI)** 07/01/2023-06/30/2024
NAU Scholarly & Creative Activity Grant $6,000
The State of the States: LGBTQ+ Inclusion in State Plans on Aging

**McCoy, M.C. (Co-Lead)** 04/26/2023-5/30/2024
SHERC Campus-Community Partnership Grant $5,000
How the dynamics between LGBTQ2S+ individuals and their peers in senior living communities affects LGBTQ2S+ care access

**Matthew Huentelman (Co-I)** 05/01/2020 – 01/31/2025
R01 AG067781 (Rogalski) $397,866 Total Project
NIH via Northwestern University
Cognitive SuperAging: A model to explore resilience and resistance to aging and Alzheimer's disease

**Matthew Huentelman (Co-I)** 09/01/2019 – 08/31/2024
W81XWH1910534 (Schwedt) $1,247,594 Total Project
DoD-CDMRP via Mayo Clinic, AZ
A multidisciplinary translational approach to investigate the mechanisms, predictors and prevention of persistent post traumatic headache.

**Matthew Huentelman (Co-I)** 10/01/2021 – 05/31/2024
U19 AG073153 (Rogalski/Geula) $4,127,147 Total Project
NIH/NIA via Northwestern University
Study to uncover pathways to exceptional cognitive resilience in aging (SUPERAging)

**Matthew Huentelman (Co-I)** 06/01/2024 – 05/31/2026
U19 AG073153 (Rogalski/Geula) $4,127,147 Total Project
NIH/NIA via University of Chicago (transfer)
Study to uncover pathways to exceptional cognitive resilience in aging (SUPERAging)

**Matthew Huentelman (Co-I)** 05/01/2021– 04/30/2026
R01 AG072643- 01 (Barnes) $1,298,796 Total Project
NIH/ University of Arizona
NPTX2: Preserving memory circuits in normative aging and Alzheimer's Disease

**Matthew Huentelman (Co-I)** 10/01/2021-03/31/2026
1R01AG069453-01 (Reiman/Caselli/Su/Chen/Langbaum) $675,696 Total Project
NIH/NIA/ via Banner Health
APOE in the Predisposition to, Protection from and Prevention of Alzheimer's Disease

**Matthew Huentelman** (Proj.1 Lead, Core D Co-L, Core G Lead) 09/01/2021 – 08/31/2026
1U19 AG056169-01A1 (Barnes) $18,509,311 Total Project
NIH via University of Arizona
Precision Aging Network: Closing the Gap Between Cognitive Healthspan and Human Lifespan

**Matthew Huentelman (Co-I)** 09/05/2021 – 06/30/2026
1 P30 AG072980-01 (Reiman) $84,470 Total Project
NIH/ Banner Health
Arizona Alzheimer's Disease Core Center

**Matthew Huentelman (Co-I)** 08/01/2022 – 07/31/2024
NIH R03AG073906 (Piras) $192,000 Total Project
Genomic determinants of sleep traits as risk and protective factors for Alzheimer's disease

**Matthew Huentelman (Co-I)** 01/01/2022 – 12/31/2025
R01HL153112 (Hale) $610,034 Total Project
NIH via University of Arizona
Targeting Resident Cardiac Fibroblast Subpopulations for Protection Against Fibrosis

**Matthew Huentelman (Co-I)** 08/15/2022 – 04/30/2027
R01AG068098 (Grilli) $199,369 Total Project
NIH via University of Arizona
Tracking autobiographical thoughts: a smartphone-based approach to identify cognitive correlates of Alzheimer's disease biomarkers and risk factors in clinically normal older adults.

**Matthew Huentelman (Co-I)** 06/15/2022 – 03/31/2027
R01AG077444 (Mesulam) $1,972,143 Total Project
NIH/ Northwestern
Asymmetric neurodegeneration and language in primary progressive aphasia

**Matthew Huentelman (PI)** 07/01/2022 – 12/31/2024
NA (Huentelman) $210,000 Total Project
City of Hope Foundation
Determining the Genetic Factors Related to Exceptional Age-related Memory

**Matthew Huentelman (PI)** 07/01/2022 – 12/31/2024
City of Hope Foundation $195,000 Total Project
Improving Brain Performance to Combat Alzheimer's

**Matthew Huentelman (PI)** 07/01/2022 – 12/31/2024
City of Hope Foundation (Huentelman) $195,000 Total Project
Identifying Genetic Risk Factors of Alzheimer's

**Matthew Huentelman (Co-I)** 03/01/2024 -02/28/2028
1R01AA030256-01A1 (Bortolato) $112,849 Total Project
NIH via University of Utah
Disentangling the biological links of violence and alcohol use.

**Matthew Huentelman (Co-I)** 09/15/2023-02/29/2025 NCE
OT2HL161847-01 (Salisbury) $157,286 Total Project
NIH via Virginia Commonwealth University
NEUROLOGICAL SEQUELAE ASSOCIATED WITH POST-ACUTE SARS-COV-2 INFECTION (NEURO-PASC)

**Matthew Huentelman (Co-I)** 09/01/2023 – 08/31/2030
5UG3OD023313 (Mitchel & D'Sa) $129,884 Total Project
NIH/Rhode Island Hospital
Assessing the cumulative risk of early life exposures on child physical health and neurodevelopment

**Matthew Huentelman (Multi-PI)** 01/12/2024 – 08/31/2026
1R01NS12331 (Sattler & Huentelman) $1,618,800 Total Project
NIH via St. Joseph's Hospital and Medical Center
Microglia contribution to disease pathogenesis in C9orf72 ALS/FTD

**Kendall Jensen/ (Co-I)** 03/01/2021 – 01/11/2024
CP18 (Berens) $462,384 Total Project
Baylor Scott & White Health Foundation
Immunologic/Transcriptomic Landscape in Glioblastoma Patients

**Kendall Jensen/ (Multi-PI)** 09/01/2021 – 01/11/2024
1R01NS12331 (Sattler & Jensen) $1,618,800 Total Project
NIH via St. Joseph's Hospital and Medical Center
Microglia contribution to disease pathogenesis in C9orf72 ALS/FTD

**Kendall Jensen/ (Co-I)** 01/15/2022 – 01/11/2024
1R01AG075059-01 (Thalacker-Mercer) $210,108 Total Project
NIH via University of Alabama at Birmingham
The essentiality of serine and glycine for skeletal muscle regeneration in aging

**Kendall Jensen/ (Multi-PI)** 03/29/2022 – 01/11/2024
MJFF-021069 (Vikas, Heutink, Craig &Jensen) $117,134 Total Project
Michael J. Fox Foundation
FOUNDIN-PD supplemental funding

**Kendall Jensen/ (PI)** 04/01/2022 – 01/11/2024
CP20 (Jensen) $912,250 Total Project
Baylor Scott & White Health Foundation
Natural Killer Cell-Derived Extracellular Vesicles as Therapeutic and Prognostic Tools in Non-Small Cell Lung Cancer

**Kendall Jensen/ (Co-I)** 09/1/2022 – 01/11/2024
R01DK133847 (Das) $650,121 Total Project
NIH/ Massachusetts General Hospital
Characterization of beta-cell-specific extracellular vesicle cargo as functional biomarkers for type 1 DM disease (TEDDY)

**Kendall Jensen/ (Co-I)** 09/1/2022 – 01/11/2024
R21NS128550 (Sattler) $18,554 Total Project
NIH via St Joseph's Hospital and Medical Center
Mechanisms of A-I RNA editing-mediated nuclear export of TDP-43

**Kendall Jensen (Co-I)** 02/16/2023 – 01/11/2024
MJF-0251971 (Ajami) $496,975 Total Project
Michael J Fox Foundation
Single-cell transcriptomics and proteomics profiling of the immune cells in the blood and cerebrospinal fluid of Parkinson's disease patients with the LRRK2 mutation.

**Kendall Jensen (Co-I)** 04/1/2023 – 01/11/2024
021821 (Cookson) $368,840 Total Project
Michael J Fox Foundation
FOUNDIN- microglial phenotypes from PPMI lines

**Kendall Jensen/ (Multi-PI)** 06/01/2023 – 01/11/2024
1R24NS132738-01 (Jensen & Eitan & Dong) $2,250,030 Total Project
A Large-scale Extracellular Vesicle RNA-seq Resource for Parkinsons Disease

**Kendall Jensen (Co-I)** 11/15/2022 – 01/11/2024
3 TO-23 (Bammas) $673,154 Total Project
Strategies to Augment Ketosis (STAK) Mild Traumatic Brain Injury (mTBI)
DoD/Florida Institute of Human and Machine Cognition

**Raffaella Soldi (Project Co-I)** 07/1/2024-06/30/2025
CTR057001 (Sharma & Soldi) $169,518 Total Project
Arizona Department of Health Services/ Arizona Alzheimer's Consortium/Banner
Identification and development of TREM2 agonists to treat Alzheimer's disease

**Sunil Sharma (PI)** 03/2020 – 09/2024
ACOHCOH2720A014 (Sharma) $2,919,263 Total Project
City of Hope National Medical Center
Gene Surgery: Small-molecule inhibitor of CDK7

**Sunil Sharma (Co- I)** 10/2019 – 09/30/2024
ATFDG012440A008 (Trent) $603,865 Total Project
Discount Tire

**Sunil Sharma (PI)** 09/2022 – 08/2024
NIH R44 CA278144 (Kaadige & Sharma) $467,258 Total Project
Development of a potent and selective oral ENPP1 inhibitor for oncology

**Sunil Sharma (Project Co-PI)** 07/2023-06/2024
CTR057001 (Sharma & Soldi) $116,666 Total Project
Arizona Department of Health Services/ Arizona Alzheimer's Consortium/Banner
A CRISPR knockout negative screen to identify genes that lead to enhancement of efficacy of antibodies targeting amyloid beta (Aβ) in Alzheimer's disease

**Sunil Sharma (Project Co-PI)** 07/2024-06/2025
CTR057001 (Sharma & Soldi) $169,518 Total Project
Arizona Department of Health Services/ Arizona Alzheimer's Consortium/Banner
Identification and development of TREM2 agonists to treat Alzheimer's disease

**Jonathan Lifshitz (PI)** 03/15/2019 – 09/30/2024
VA Merit I01 RX002472 $1,100,000 Total Project
U.S. Dept. of Veterans Affairs
Brain Injury Rehabilitation Modality, Regulation, & Structural Plasticity

**Jonathan Lifshitz (PI)** 12/01/2020 – 09/30/2024
VA Merit I01 RX002472 $526,529 Total Project
U.S. Dept. of Veterans Affairs
Developing and Testing a Novel Virtual Cognitive Rehabilitation Program to Alleviate Persistent Cognitive Dysfunction Following Traumatic Brain Injury

**Raymond Migrino and Jonathan Lifshitz (dual PI)** 04/01/2021 – 03/31/2025
VA Merit I01002691 $1,200,000 Total Project
U.S. Dept. of Veterans Affairs
Mechanistic role of vascular dysfunction in TBI-mediated cognitive dysfunction

**Jonathan Lifshitz (PI)** 10/01/2021 – 09/30/2023
NCL-TBI-2021-011 $314,836 Total Project
Neurotrauma Sciences, LLC
Sleep, inflammation and therapeutic efficacy of NTS-104 in diffuse TBI

**Jonathan Lifshitz (PI)** 04/01/2023 – 03/31/2025
NIH/NINDS R21 NS131877 $422,125 Total Project
Miniscope in vivo imaging of cumulative traumatic brain injury

**Jonathan Lifshitz and Sarah Stabenfeldt (dual PI)** 04/01/2023 – 12/31/2026
NIH/NIA R01 AG077768 $2,951,028 Total Project
Molecular Tool Development to Identify, Isolate, and Interrogate the Rod Microglia Phenotype in Neurological Disease and Injury

**Jonathan Lifshitz (PI)** 10/1/2023 – 09/30/2027
VA Merit I01 RX004536 $1,200,000 Total Project
U.S. Dept. of Veterans Affairs
Psychoplastogens to make the injured brain receptive to cognitive rehabilitation during the chronic period of TBI

**Gene E. Alexander (MPI)** 08/01/2019 – 04/30/2025
NCE $3,797,247 TC
NIA R01 AG064587 (MPIs: Alexander, Bowers, Woods)
Revitalizing Cognition in Older Adults at Risk for Alzheimer's Disease with Near-Infrared Photobiomodulation

**Gene E. Alexander (Core Leader)** 09/01/2021 - 06/30/2026
NIA P30AG072980 (PI: Reiman, Core Leader: Alexander) $1,223,160 TC UA Sub
Arizona Alzheimer’s Disease Research Center

**Gene E. Alexander (MPI)** 04/01/2021-03/31/2026
NIA R01AG072445 (MPIs: Raichlen, Alexander, Klimentidis) $3,074,021 TC
Inactivity, Sedentary Behavior, and the Risk for Alzheimer’s Disease in Middle Aged to Older Adults

**Gene E. Alexander (MPI)** 05/01/2018-04/30/2025 NCE
(MPIs: Alexander, Bowers, Woods) $120,000 TC
McKnight Brain Research Foundation
A Pilot Intervention with Near Infrared Stimulation: Revitalizing Cognition in Older Adults

**Gene E. Alexander (PI UA Sub)** 10/01/2019-09/30/2024 NCE
(PI UA Sub: Alexander, PI: Williamson) $30,000 TC UA Sub
McKnight Brain Research Foundation
Transcutaneous Vagal Nerve Stimulation and Cognitive Training to Enhance

**Gene E. Alexander (PI)** 07/01/2024-06/30/2025
(PI: Alexander) $33,000 TC
State of Arizona
Brain/Body Network Imaging and Lifestyle Behavioral Biomarkers of Brain Aging and Alzheimer’s Disease

**Gene E. Alexander (Co-I)** 09/01/2019-08/31/2025 NCE
NIA R01AG061888 (PI: Wilson) $1,765,250 TC
Evaluating the Neurocomputational Mechanisms of Explore-Exploit Decision Making in Older Adults

**Gene E. Alexander (Co-I)** 05/01/2020-04/31/2025
NIA R01AG062543 (PI: Chou) $3,546,144 TC
Enhancement of Hippocampal Plasticity Using Repetitive Transcranial Magnetic Stimulation

**Gene E. Alexander (Co-I)** 08/15/2021-05/31/2026
NIA R01AG070987 (PI: Weinkauf) $4,900,635 TC
Extracranial Carotid Atherosclerosis Contributions to Cognitive Impairment and Alzheimer's Disease Risk

**Gene E. Alexander (Co-I)** 07/01/2022-06/30/2027
NIA R01AG068098 (MPIs: Andrews-Hanna, Grilli) $4,600,829 TC
Tracking autobiographical thoughts: a smartphone-based approach to identifying cognitive correlates of Alzheimer's disease biomarkers and risk factors in clinically normal older adults

**Maria Altbach (PI)** 09/01/2021-08/31/2022
R01 HL159200 (Altbach, DeMarco, Li, Parker, Saloner) $6,156,398 total project
NIH/NHLBI
Multi-Center Implementation and Validation of Efficient Magnetic Resonance Imaging and Analysis of Atherosclerotic Disease of the Cervical Carotid.

**Maria Altbach (PI)** 07/01/2021-06/31/2025
CTR056039 (Altbach, Bilgin) $750,000 total project
Arizona Biomedical Research Commission
Development of MRI Biomarkers for Improved Risk Stratification of Patients with Carotid Atherosclerosis to Prevent Stroke.

**Maria Altbach (Co-I)** 10/01/2020-09/30/2024
I01 CX002208-01 (Treiman) $4,909,447 total project
Veterans Affair Administration
Development of a practical quantitative non-contrast approach for cerebrovascular MRI.

**Maria Altbach (PI)** 08/01/2022-04/30/2027
U01 EB031894 (Altbach, Deshpande, Wu) $3,533,177 total project
NIH/NIBIB
Quantitative MRI and Deep Learning Technologies for Classification of NAFLD

**Maria Altbach (PI)** 12/01/2019-11/30/2024
R01 CA245920 (Altbach, Martin) $2,207,955 total project
NIH/NCI
Advancing MRI technology for early diagnosis of liver metastases.

**Maria Altbach (Co-I)** 04/01/2024-03/31/2027
RFGA2023-008-12 (Chen) $750,000 total project
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.

**Jessica Andrews-Hanna (MPI) and David Sbarra (MPI)** 04/01/2021-01/26/2026
R01 MH125414-01 $2,947,569 Total Project
NIH/NIMH

**Carol Barnes (PI)** 09/01/2021-08/31/2026
NIH/NIA U19 AG0165169 $60,000,000 Total Project
Precision Aging Network: Closing the Gap Between Cognitive Healthspan and Human Lifespan

**Carol Barnes (PI)** 07/01/2023-06/30/2024
Arizona Alzheimer's Research Center $36,094 Direct Costs
Assessment of the relation between microbiome composition, dietary habits, and cognitive status in a cognitively well-characterized cohort of older adults

**Carol Barnes (PI), Stephen Cowen (Co-I)** 05/15/2023-04/30/2028
NIH/NIA 5 R01 AG031581 (Barnes/Cowen) $3,266,421 Total Project
Frontal and Temporal Lobe Interactions in Rat Models of Normative Aging and Alzheimer's Disease

**Ying-hui Chou (PI)** 05/2020-01/2025
NIH R01AG062543 $3,400,705 Total Award
Enhancement of Hippocampal Plasticity Using Repetitive Transcranial Magnetic Stimulation

**Ying-hui Chou (MPI) and Robert Wilson (MPI)** 01/2020-12/2024
NIH R01AG061888 $1,726,875 Total Award
Evaluating the Neurocomputational Mechanisms of Explore-Exploit Decision Making in Older Adults

**Ying-hui Chou (MPI) and R Witte (MPI)** 09/2020-06/2025
NIH/NIBIB U01EB029834 $3,414,477 Total Award
Transcranial Acoustoelectric Imaging for High Resolution Functional Mapping of Neuronal Currents

**Ying-hui Chou (MPI) and Lee Ryan (MPI)** 07/2023-06/2024
019826-00021 $31,000 Total Award
Arizona Alzheimer's Consortium | ADHS
AAC FY24: Investigating Gut Microbiome in Individuals with Mild Cognitive Impairment

**Stephen Cowen (Co-I)** 08/01/2023-08/31/2024
R43 OD034043-01A1 (Gibson/Cowen) $256,488 Total Project
NIH/SBIR Development of in-cage health monitoring system for laboratory animals.

**Stephen Cowen (Co-I)** 07/01/2021-06/31/2026
P30 NIH-NIDA 3042524 (Porreca is lead) $6,422,364 Total Project
NIH/NIDA Core Center of Excellence in Addiction Studies

**Stephen Cowen (PI)** 08/01/2021-07/31/2026
R01NS123424-01 (Cowen/Heien/Lewis) $1,833,908 Total Project
NIH BRAIN Initiative
Control of the time course of dopamine release through optimized electrical brain stimulation.

**Stephen Cowen (Co-I)** 07/01/2021-06/30/2025
5R01NS122805-03 (Falk) $1,861,435 Total Project
Mechanisms of low-dose ketamine treatment for Parkinson's disease

**Arne Ekstrom (PI) and Matthew Grilli (Co-I)** 06/2020-05/2025
R01NS114913 $2,769,521 Total Project
NIH/NINDS

**Arne Ekstrom (PI) and Matthew Grilli (Co-I)** 05/2023-01/2025
R21AG081558 $422,125 Total Project
NIH/NIA

**Arne Ekstrom (PI) and Jessica Andrews-Hanna (Co-I)** 06/15/2020-05/31/2025
R01NS109819 $3,416,596 Total Project
NIH/NINDS

**Matthew Grilli (MPI) and Jessica Andrews-Hanna (MPI)** 08/2022-04/2027
R01AG068098 $4,649,591 Total Project
NIH/NIA

**Meredith Hay, (PI)** 09/01/2023-08/31/2027
U01AG082617 (Hay) $7,954,818
University of Arizona
PNA5: A Novel Mas Receptor Agonist for Treatment of Cognitive Impairment in Patients at Risk for Vascular Dementia and Alzheimer's Disease Related Dementia: an FDA required Toxicology Study

**Meredith Hay, (PI)** 04/01/2000-03/31/2025
5U01AG066623-04 (Hay) $6,705,000
University of Arizona
“IND-enabling studies for a novel Mas receptor agonist for treatment of cognitive impairment in patients at risk for Alzheimer’s disease related dementia”

**Elizabeth Hutchinson (PI)** 06/01/2023-05/31/2028
R01 AG079280 (Frank/Hutchinson/Bondi) $7,691,496 Total Project
NIH/NIA
Joint Estimation Diffusion Imaging (JEDI) for Improved Tissue Characterization and Neural Connectivity in Aging and Alzheimer's Disease

**Elizabeth Hutchinson (Co-I)** 12/01/2024-11/30/2029
CNRM Core Funding Awards (Juliano) $99,569 Total Subaward
DoD
Translational Therapeutic Ferret Core

**Elizabeth Hutchinson (Co-I)** 06/01/2024-05/31/2028
DARPA Cornerstone Broad Area Announcement (Battelle) $99,569 Total Subaward
DoD
A Military-Relevant Brain Injury Model in a Gyrencephalic Animal with Therapeutic Investigation

**Elizabeth Hutchinson (Co-I)** 07/01/2022-06/30/2027
R01 AG073230 (Pires) $1,367,466 Total Project
NIH/NIA
Role of Endothelial K+ Channels in Age-Related Dementia

**Elizabeth Hutchinson (Co-I)** 09/01/2023-08/31/2028
NIH R01 MH135267 (Gothard) $2,819,927 Total Project
Maturation of social and non-social reward processing in the adolescent amygdala and orbitofrontal cortex

**Kathleen Insel (PI) and Matthew Grilli (Co-I)** 05/2022-04/2025
R01NR020261 $2,555,971 Total Project
NIH/NINR

**Aneta Kielar (PI)** 01/15/2024-12/31/2028
NIH/NIA $3,755,306 Total Project
Enhancing Language in Logopenic Primary Progressive Aphasia with Targeted Phonological Treatment and Transcranial Direct Current Stimulation (tDCS)

**Aneta Kielar (PI)** 07/01/2024-01/31/2024
NIA via Arizona Alzheimer's Consortium $162,252 Total Project
Using Noninvasive Electrical Brain Stimulation to Improve Language in the Logopenic variant of Alzheimer's Disease

**Francisco Moreno (PI) and Andrews-Hanna (Co-I)** 09/01/2024-08/31/2029
TBD $500,000 Total Project
International OCD Foundation

**Lee Ryan (Project Lead)** 09/01/2021-08/31/2026
U19 AG065169 (Barnes) $12,472,457 Total Project
NIH/NIA
Precision Aging Network: Closing the Gap Between Cognitive Healthspan and Human Lifespan

**Lee Ryan (Co-I)** 05/24/2021-05/23/2025
NIH/NHLBI OT2HL161847 (Katz) $10,450,019 Total Project
NIH RECOVER: A Multi-site Observational Study of Post-Acute Sequelae of SARS-CoV-2 Infection in Adults (Initiative: REsearching COVid to Enhance Recovery (RECOVER) Initiative)

**Lee Ryan (Co-I)** 05/01/2020-04/30/2025
R01 AG062543 (Chou) $678,098 Total Project
NIH/NIA
Enhancement of Hippocampal Plasticity Using Repetitive Transcranial Magnetic Stimulation

**Lee Ryan (PI)** 07/01/2023-06/30/2024
Arizona Department of Health Services, AAC $39,280 Total Project
Psychosocial stress and diurnal cortisol profiles: Examining biological pathways of cognitive health disparities among older adult Latinos and non-Hispanic Whites

**Lee Ryan (Co-I)** 09/01/2023-08/31/2027
TP220092 (Joseph) $3,004,651 Total Project
DoD
Angiotensin-(1-7): A Treatment for Neuropsychological and Memory Impairments Following Moderate to Severe Traumatic Brain Injury

**David Sbarra (PI) and Matthew Grilli (Co-I)** 08/2022-04/2027
R01AG078361 $5,466,453 Total Project
NIH/NIA

**Judith Su (PI)** 01/15/2023-12/31/2027
2237077 (Su) $500,000 Total Project
CAREER: Bioinspired optical sniffer based on microtoroid resonators and science and technology convergence

**Judith Su (PI)** 09/01/2020-08/31/2025
NIH/NIGMS 1R35GM137988 $1,822,950 Total Project
Label-free single molecule detection for basic science and translational medicine

**Judith Su (PI)** 08/01/2018-05/30/2024
12326236 $2,790,212 Total Project
Defense Threat Reduction Agency (DTRA)
Sensitive, Selective, and Affordable Chemical Threat Sensing Using Frequency Locked Microtoroid Optical Resonators

**Judith Su (PI of subcontract)** 01/15/2024-12/31/2024
NSF via UCLA 2344350 $100,000 Total Project
NSF Convergence Accelerator Track L: Portable Quantum-enhanced Sensing and Species Identification of Bioaerosols

**Daniel Taylor (PI) and Matthew Grilli (Co-I)** 08/2023-08/2029
GRANT13453862-PR210654 $6,322,300 Total Project
DoD

**Trouard (Co-I)** 04/01/2024-03/31/2027
ABRC (PI:Nk Chen) $750,000 Total Project
Development of high-performance, low cost, low field MRI to improve care in lung cancer and respiratory illnesses

**Trouard (PI)** 03/15/2023-03/14/2025
S10 OD032166 (Trouard) $2,000,000 Total Project
NIH/NIA via University of Arizona
3T MRI scanner for Advanced Brain Imaging

**Trouard (Co-I)** 07/01/2021-06/30/2026
U19 AG065169 (Barnes) $60,014,605 Total Project
NIH/NIA via University of Arizona
Precision Aging Network: Closing the Gap Between Cognitive Healthspan and Human Lifespan

**Trouard (Co-I)** 09/01/2021-06/30/2026
P30 AG072980 (Alexander, Reiman) $1,223,160 Total Project
NIH/NIA via University of Arizona
Arizona Alzheimer’s Disease Research Center

**Craig Weinkauf (PI)** 10/01/2020-09/30/2024
NIH/NIA R01 AG070987 (Weinkauf) $1,200,000 total project
Extracranial Carotid Atherosclerosis Contributions to Cognitive Impairment and Alzheimer’s Disease Risk

**Craig Weinkauf (PI)** 08/20/2023-05/31/2026
NIH/NIA R01 AG070987-S1 (Weinkauf) $382,766
Extracranial Carotid Atherosclerosis Contributions to Cognitive Impairment and Alzheimer's Disease Risk

**Robert Wilson (PI) and Jessica Andrews-Hanna (Co-I)** 09/01/2019-08/31/2024
R01 AG061888 $1,765,250 Total Project
R01/NIA

**Fei Yin (PI)** 05/15/2021-04/30/2026
NIH/NIA RF1 AG068175 (Yin) $1,881,282 Total Cost
ApoE Regulation of Neuron-Astrocyte Metabolic Coupling in Alzheimer's Disease

**Fei Yin (PI)** 05/01/2024-04/30/2029
NIH/NIA RF1 AG079157 (Yin) $2,692,015 Total Cost
Disrupted Lipid Metabolism in Alzheimer's Disease

**Fei Yin (Project Leader)** 04/01/2021-05/31/2026
P01 AG026572 (Brinton) $15,168,816 Total
NIH/NIA $1,712,931 Project 1
Perimenopause in Brain Aging and Alzheimer's Disease
Project 1: Metabolic Mechanisms of Perimenopausal Neuroimmune Transformation: Therapeutic Targets and Windows

**Fei Yin (Core Leader)** 04/01/2021-05/31/2026
P01 AG026572 (Brinton) $15,168,816 Total
NIH/NIA $2,282,929 Analytic Core
Perimenopause in Brain Aging and Alzheimer's Disease
Analytic Core

**Fei Yin (Subcontract PI)** 09/01/2022-08/31/2024
R44 AG078102-01A1 (Rinehart) $614,889 Subcontract
NIH/NIA via NeuTherapeutics, LLC
PhytoSERM for Menopausal Hot Flashes and Sustained Brain Health

**Fei Yin (Co-I)** 04/15/2022-03/31/2027
NIH/NIA R37 AG053589 (Brinton) $2,686,250 Total Project
Aging and Estrogenic Control of the Bioenergetic System in Brain

**Fei Yin (Co-I)** 07/01/2022-06/30/2027
NIH/NIA U01 AG076450 (Thatcher) $3,799,050 Total Project
Nonlipogenic ABCA1 inducers for ADRD

**Fei Yin (Co-I)** 09/01/2018-05/31/2024
NIH/NIA R01 AG057931 (Brinon/Mosconi/Chang) $6,006,958 Total Project
Sex Differences in the Molecular Determinants of Alzheimer's Disease Risk: Prodromal Endophenotype

**Fei Yin (Subcontract PI)** 04/15/2022-05/31/2024
R21 AG072561 (Gu) $76,750 Total Project
NIH/NIA via ASU
Targeting Whole-body Fatty Acid Metabolism in Alzheimer's Disease, with Special Interest in Lauric acid

**Fei Yin (Co-I)** 08/01/2018-03/31/2023
RF1 AG057931 (Kaddurah-Daouk/Brinton/Kastenmuller/Chang) $640,519 Total Project
NIH/NIA via Duke University
Metabolic Networks and Pathways Predictive of Sex Differences in AD Risk and Responsiveness to Treatment

**Zhou, MPI** 04/01/2023-03/31/2028
U01 DK119094 NIH-NIDDK (Gurtner/Zhou) $2,559,641 Total Project
The University of Arizona Wound Care Center Clinical Research Unit

**Zhou, PI** 11/01/2023-10/31/2024
Cardiovascular Research/Diabetes Research Award 5785200-24WZ
Saver Heart Center
Understanding Diabetic Lipid Signature in Plaque Vulnerability

**Zhou, Site-PI** 03/01/2017-02/28/2028
UNA-224063-01/U01NS080168 $338,600 Total Project
NIH-NINDS Brott/Lal/Meschia (MPI)
Carotid Revascularization and Medical Therapy for Asymptomatic Carotid Stenosis Trial

**Zhou, Site-PI** 05/01/2019-04/30/2028
R01NS097876 $32,900 (subaward) Total
NIH-NINDS Marshall/Connolly/Lazar/Liebeskind (MPI)
Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial - Hemodynamics (CREST-H)

**Heather Bimonte-Nelson (PI)** 06/01/2016 – 05/31/2025
R01AG028084 $2,362,615 Total Project
NIH/NIA
Variations in Hormones During Menopause - Effects on Cognitive and Brain Aging

**Heather Bimonte-Nelson (Co-I)** 09/05/2021 – 06/30/2026
NIH/NIA P30AG072980 (Reiman, PI) $15,727,544 Total Project
Arizona Alzheimer's Disease Research Center (ADRC)

**Heather Bimonte-Nelson (Subcontract PI)** 09/30/2022 – 08/31/2024
R21DA055879 (Gipson-Reichardt, PI) $34,038 Subcontract
University of Kentucky via NIH/NIDA
Contributions of Progestins Independently and Interactively with Contraceptive Estrogen to Nicotine Use

**Heather Bimonte-Nelson (Co-I)** 01/01/2021 – 11/30/2025
NIH R01NS116647, Stabenfeldt (PI) $1,491,063 Total Project
Exploiting Sex-dependent Brain Injury Response for Nanoparticle Therapeutics

**Heather Bimonte-Nelson (Sub-Project PI)** 07/01/2023 – 06/31/2024
LTR 7/1/23, Coon (PI) $365,000 Total Project
Arizona Department of Health Services/Arizona Alzheimer's Consortium: Evaluation of Clinically-Used Progestogens on Cognition During the Transition to Menopause in the Rat (Arizona Alzheimer's Consortium (AAC) FY24 Projects)

**Heather Bimonte-Nelson (Sub-Project PI)** 07/01/2024 – 06/31/2025
LTR 6/24/24, Coon (PI) $365,000 Total Project
Arizona Department of Health Services/Arizona Alzheimer's Consortium: Evaluations of Aging and Surgical Menopause on a Battery of High-Load Memory Tasks: Relationships with Systemic Immune Markers, Neuroinflammation, and Neurovasculature (Alzheimer's Consortium (AAC) FY25 Projects)

**David Brafman (PI)** 08/04/2023-08/03/2025
Department of Defense, 2021-01T-T026 $1,522,000 Total Cost
Development of Low-Cost, Paper-Based System for the Detection of Adventitious Agents in Biomanufacturing Processes

**David Brafman (PI)** 07/01/2023-06/30/2024
NIH-OD, 1R24OD035477-01 $59,684 Total Cost
Acquisition of an Automated Tissue Processor for the ASU Shared Imaging Core Facility

**David Brafman (PI)** 07/01/2023-06/30/2024
Arizona Alzheimer's Disease Consortium $45,000 Total Cost
FY 2024 AADC: Investigating an African American-specific APOE variant using hiPSC

**David Brafman (PI)** 01/01/2023-12/31/2025
Alzheimer's Association, AARG-22- 973218 $300,000 Total Cost
Investigating the protective mechanisms of APOE2

**David Brafman (PI)** 08/01/2022-07/31/2025
NIH-NIA, 1 R21 AG079279-01 $431,750 Total Cost
Establishing Genotype-to-Phenotype Relationships Between Alzheimer's Related BIN1 Variants

**David Brafman (PI)** 08/01/2022-07/31/2023
NIH-OD, 1 S10 OD032287-01 $599,268 Total Cost
BD FACSymphony S6 cell sorter

**David Brafman (PI)** 02/01/2022-01/31/2025
NIH-NIA, 1 R21 AG075612-01 $431,750 Total Cost
Elucidating the protective effects of the KL-VS variant using isogenic hiPSCs

**David Brafman (PI)** 02/01/2022-01/31/2023
Edson Foundation New Idea Award $112,671 Total Cost
Using CRISPR-based genome approaches to investigate the interactions between APOE and CLU risk variants

**David Brafman (PI)** 10/01/2021-10/01/2024
Alzheimer's Association, AARG-21-851005 $150,000 Total Cost
Investigating African American-specific ABCA7 variants using hiPSCs

## CURRENT & PENDING GRANTS

**David Brafman (PI)** 09/30/2021-08/31/2024
NIH-NIA, R21 AG07040 $431,750 Total Cost
Using hiPSCs to investigate the protective mechanisms of the ApoEch mutation

**David Brafman (PI)** 04/09/2020-03/21/2025
Glen Swette Memorial Funds $310,526 Total Cost
Swette Young Investigator in ALS

**Cheryl Conrad (Sub-project PI)** 07/01/2023 – 06/31/2024
LTR 7/1/23, Coon (PI) $365,000 Total Award
Arizona Department of Health Services/Arizona Alzheimer's Consortium
Age and Chronic Stress Interactions on Memory and Anxiety in Female Rats (Arizona Alzheimer's Consortium (AAC) FY24 Match Projects)

**Cheryl Conrad (Sub-project PI)** 07/01/2024 – 06/31/2025
LTR 6/24/24, Coon (PI) $365,000 Total Award
Arizona Department of Health Services/Arizona Alzheimer's Consortium
Age and Chronic Stress Interactions on Depressive Behavior and Brain Plasticity in Female Ovariectomized Rats
Alzheimer's Consortium (AAC) FY25 Match Projects)

**David W. Coon (Sub-contract PI)** 9/1/2023-1/31/2025
Halle Foundation $60,000 Total ASU
The CHANGE Pilot Program for Aging Residents: A Community Health Navigation Program.
Parent award to Foundation for Senior Living

**David W. Coon (Co-I)** 4/1/2023-3/31/2028
NIH (Fang Yu, PI) $4.7 million
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 Responses

**David W. Coon (Sub-contract PI)** 9/30/2021-8/31/2026
NIA (Carol Barnes, PI) $2.11 million (ASU only)
Precision Aging Network: Closing the Gap between Cognitive Healthspan and Human Lifespan

**David W. Coon** 07/01/21 – 06/30/26
NIA – P30 ADRC (ORE Core) $15.7 million Total
Arizona Alzheimer's Disease Research Center

**David W. Coon (Mentor)** 9/1/2022-6/30/2027
NIH (DeAnnah Byrd, PI) $630,329
The Epidemiology of Cognitive Decline in African Americans: Identifying Risk and Protective Factors (K01)

**David W. Coon (Co-PI)** 10/1/2022- 9/30/2024
National Endowment for the Arts $160,000 Total ASU
NEA Research Lab Renewal (Tamara Underiner, Co-PI)

**Candace Lewis (PI)** 5/6/2022 – 03/31/2025
NIH AWD00037259 $496,220
Host DNA methylation as a mechanism of microbiome influence on behavior

## CURRENT & PENDING GRANTS

**Candace Lewis (PI)** 8/1/2023 – 7/31/2025
AWD00038661 $125,000
Institute for Mental Health Research; Arizona State University Foundation
Isolating Environmentally induced DNA methylation patterns

**Eleni Panagiotou (PI)** 07/01/2024-06/30/2025
ASU Women in Philanthropy $49,096 Total Project
Mathematics in the fight against Alzheimer's disease

**Eleni Panagiotou (PI)** 09/01/2023-08/31/2026
R01 GM152735 NIGMS $589,351 Total Project
Topological dynamics models of protein function

**Eleni Panagiotou (PI)** 08/01/2019-07/30/2026
NSF CAREER 2047587 $537,785 Total Project
Entanglement of active polymers

**Eleni Panagiotou (PI initially, now co-PI)** 09/30/2016-07/30/2024
NSF RUI 1913180 $125,000 Total Project
Computational methods for measuring entanglement in polymers

**Eleni Panagiotou (co-PI)** 05/01/2022-04/30/2025
NSF 1925603 $392,235 Total Project
CC* Compute: Augmenting a 2,560-core EPYC2 Computational Cluster with GPUs for AI, Machine Learning and other GPU- Accelerated HPC Applications

**Heather Ross, PI; Diana Bowman, Co-PI** 01/01/2024 – 09/30/2024
LTR 1/1/2024, PI: Ross $35,000
Piper (Virginia G.) Charitable Trust – ASU: Knowledge Exchange for Resilience Building
Resilience Through Better Sleep in Homeless Shelters

**Heather Ross, PI; Diana Bowman, Co-PI** 07/01/2023 – 06/30/2024
LTR 7/21/23, PI: Ross $35,000
Arizona Department of Health Services (ADHS) – Arizona Alzheimer's Consortium
Arizona Alzheimer's Consortium (AAC) FY24 Match Projects: Dementia and Mild Cognitive Impairment in Adults Experiencing Homelessness

**Diana Bowman, Co-PI** 01/01/2023 – 12/31/2026
2228782, PI: Neithalath $3,000,000
National Science Foundation
FMRG: Eco: Reimagining Cement Manufacturing for Carbon Neutrality (NeutraCEM)

**Heather Ross, subaward PI** 01/01/2024 – 12/31/2024
FP00041444, PI: Taylor (City of Phoenix) $139,560
Department of Justice: Community Oriented Policing Services – City of Phoenix
Beyond Alternatives to Police: Identifying Barriers to Mental Health Treatment in Maricopa County to Reduce Police Involvement

**Heather Ross, PI** 10/1/2023 – 01/31/2025
G11236-300 PI: Ross $90,000
New Venture Fund (NVF) – Arizona State University Foundation ASU-N Public Interest Technology (PIT) for Homeless Shelters

**Heather Ross, Co-I** 01/01/2023 – 05/31/2024
C-86-23-088-X-00; P, PI: Carr-Jordan $1,000,000
HHS: Centers for Disease Control and Prevention (CDC) – AZ-M Telehealth Pilot Program

**Heather Ross, PI** 12/01/2020 – 06/30/2024
AWD00036525, PI: Ross $56,250 (sub of main award)
Tonoho O'Odham Nation – AZ: City of Tempe
Culturally Relevant Low Literacy Digital Education to Increase COVID Vaccination in Vulnerable Arizona Populations

**Heather Ross, Co-I** 06/01/2024 – 05/31/2027
2324-GJ-0501SCG-106; PI: Scharf (CASS) $175,000
Vitalyst Health Foundation
FY2324 Central Arizona Shelter Services Systems Change Grant

**Sydney Schaefer (PI)** 07/01/2024 – 06/30/2026
ARCOM-24-1251824 $249,825
Alzheimer's Association
Towards an equitable alternative for early Alzheimer's disease screening

**Sydney Schaefer (Co-I)** 10/01/2023 – 09/30/2024
NIA R43 AG082604-01A1 (PI: Jill Love) $369,939
Neurosessments: Developing a quick, objective motor test to prompt cognitive testing in primary care

**Sydney Schaefer (PI)** 09/01/2023 – 08/31/2025
R21 AT012088-01A1 $436,303
National Center for Complementary and Integrative Health
Measuring Expectancy Effects of Transcranial Direct Current Stimulation on Motor Learning

**Sydney Schaefer (PI)** 07/1/2023 – 06/30/2024
Edson Initiative for Dementia Care and Solutions $124,740
Biodesign Institute, Arizona State University. Comparing state anxiety between cognitive and motor testing among older adults to advance earlier dementia screening

**Sydney Schaefer (Primary Sponsor)** 01/01/2022 – 12/31/2024
F32 AG071110-01A1 (PI: Andrew Hooyman) $211,182
National Institute on Aging
Using an Online Video Game to Predict Functional and Cognitive Decline within the MindCrowd Electronic Cohort

**Nina Sharp (PI)** 07/01/2023 – 12/31/2024
Edson Initiative Seed Grant (Sharp) $119,885 Total Project
Building IoT: Development of a Patient-specific Thermal and Lighting Environment Control Framework for the Patient's Cognitive Performance and Well-being in the Dementia Care

**Michael Sierks (PI)** 01/30/2022-08/31/2024
R43 AG076091 (Sierks) $26,993 Total Project
NIH via Virtici
A Novel Multiparameter Blood Test for Early Detection of Alzheimer's Disease

**Michael Sierks (PI)** 09/01/2021-08/31/2024
W81XWH2110837 (Sierks) $1,295,595 Total Project
DOD-ARMY: Army Medical Research Acquisition Activity Targeting Toxic Oligomeric Protein Variants Generated after Traumatic Brain Injury to Decrease Risk of AD

**Michael Sierks (PI)** 8/1/2022 - 7/31/2024
1R21AG079095-01 (Sierks) NIH $431,750 Total Project
Purification and Characterization of a toxic AD associated intracellularly generated amyloid beta fragment

**Michael Sierks (PD/PI)** 07/01/2023–06/30/2024
LTR 7/21/23 (Coon) AWD38742 $42,500
AAC FY24: Intracellular Targeting of Toxic Tau Variants as a novel treatment for Alzheimer's Disease

**Sarah Stabenfeldt (PI)** 01/01/2021-11/30/2025
R01 NS116657 (Stabenfeldt/Sirianni) NIH/NINDS $2,551,485
Exploiting sex-dependent brain injury response for nanoparticle therapeutics

**Sarah Stabenfeldt (PI)** 08/15/2021-07/31/2024
R03 NS122018 (Stabenfeldt/Bowser) NIH/NINDS $100,000
Linking TBI secondary injuries to FTLD- and ALS-like neurodegeneration

**Sarah Stabenfeldt (PI)** 10/01/2022-09/30/2024
W81XWH-22-1-0388 CDMRP (Acharya) DOD – ARMY $300,000
Developing vaccines for immunological defense from traumatic brain injury

**Sarah Stabenfeldt (MPI)** 04/01/2023-12/31/2026
R01 AG077768-01 (Lifshitz/Stabenfeldt) $2,842,247
NIH/NIA – by way of Phoenix VA
Molecular tool development to identify, isolate, and interrogate rod microglial

**Sarah Stabenfeldt (Co-I)** 04/01/2023-03/31/2027
1R01HL162809 (Brown) NIH/NHLBI $2,360,944
Anti-microbial platelet-like-particles to treat internal bleeding and augment subsequent healing

**Sarah Stabenfeldt (Co-I)** 07/01/2023-06/30/2026
R01 GM145916 (Stephanopoulos/Sulc) NIH/NIGMS $1,316,241
Multivalent protein-DNA nanostructures as synthetic blocking antibodies

**David Coon (PI): Verpeut: Sub-Project PI** 7/1/2024 – 6/30/2025
LTR 6/24/24 (Coon) $365,000 Total Project
ADHS, Arizona Alzheimer's Consortium (AAC) FY25 Match Projects
Identifying neural mechanisms underlying behavior during aging in the TgF344-AD rat, a preclinical Alzheimer's disease model

**Jessica Verpeut (PI)** 6/01/2023-8/31/2024
AGR 5/25/2023, Verpeut $50,000 Total Project
Institute for Mental Health Research
Neural mechanisms underlying social and cognitive behavior in autism: The role of cerebellar-mPFC connections

**David Coon (PI); Verpeut: Sub-Project PI** 7/01/2023-6/30/2024
LTR 7/21/23 $365,000 Total Project
ADHS, Arizona Alzheimer's Consortium (AAC) FY24 Match Projects
Guidance of learning and reversal ability by neural complexity in cognitive-associated brain regions of juvenile and middle-aged mice.

**Reiman (PI): Verpeut: Co-I** 09/05/2021-6/30/2026
P30 AG072980, NIH $15,727,544 Total Project
Arizona Alzheimer’s Disease Research Center (Arizona Alzheimer's Consortium REC Fellow)
NIH/NIA via Arizona State University
Cerebellar circuits in aging and autism spectrum disorder: a study across the lifespan.

**Jessica Verpeut (PI)** Spring 2024
Institute for Social Science Research $8,000 Total Project
Arizona State University (internal)
Examining cerebellar nuclei pathways in social behavior

**Yalin Wang (MPI)** 8/1/2021-8/31/2025
R01EY032125 (Wang/Lu) $1,559,565.00
HHS: National Institutes of Health (NIH)
Hierarchical Bayesian Analysis of Retinotopic Maps of the Human Visual Cortex with Conformal Geometry

**Yalin Wang (PI)** 9/15/2021 – 5/31/2026
R01DE030286 (Lepore) $230,192.00
Children’s Hospital Los Angeles
Early Joint Cranial and Brain Development from Fetal and Pediatric Imaging

**Melissa Wilson, PI** 06/01/2023 - 03/31/20218
2R35GM124827, Wilson $2.1M
NIH NIGMS
Population dynamics and medical consequences of sex chromosome evolution

**David Weidman (Co-I)** 01/01/2021-08/31/2023
NIH R42AG053149 via MS Technologies (Lure) $237,162
Multi-Modality Image Data Fusion and Machine Learning Approaches for Personalized Diagnostics and Prognostics of MCI due to AD

**David Weidman (Project PI)** 07/01/2023-06/30/2024
Arizona DHS via Arizona Alzheimer’s Consortium $60,000
Native American Outreach, Recruitment, and Retention Program

**David Weidman (Site PI)** 07/01/2021-06/30/2026
NIH/NIA via ASU P30AG072980 (Reiman) $15,077,717
Arizona Alzheimer’s Disease Research Center – Clinical Core

**David Weidman (Site PI)** 05/01/2019-04/30/2024
NIH/NIA via USC (ATRI) R01 AG053798 (Aisen) $80,000
Global Alzheimer's Platform Trial-Ready Cohort for Preclinical/Prodromal Alzheimer's Disease

**Don Saner (Co-I)** 09/30/2020-03/31/2026
NIH/NIA R01 AG069453 (Reiman/Su/Langbaum/Woodruff) $27,473,070
APOE in the Predisposition to, Protection from and Prevention of Alzheimer's Disease

**Don Saner (Co-I)** 09/01/2018-11/30/2024
NIH/NIA $32,005,950
R01AG058468 (Reiman/Aisen/Johnson/Langbaum/Sperling/ Tariot)
API / A4 Alzheimer's Prevention Trial

**Don Saner (Co-I)** 04/01/2017-03/31/2024
NIH/NIA $14,893,051
R01 AG055444 (Reiman/Tariot/Lopera)
Alzheimer's Prevention Initiative ADAD Colombia Trial

**Don Saner (Core Co-Leader)** 09/05/2021-06/30/2026
NIH/NIA via ASU P30AG072980 (Reiman) $15,077,717
Arizona Alzheimer's Disease Research Center – Data Management & Statistics Core

**Don Saner (Project PI)** 07/01/2023-06/30/2024
Arizona DHS via Arizona Alzheimer's Consortium $50,000
Enhancements to a Centralized Data Management System for the Arizona Alzheimer's Disease Core Center (ADCC), Brain and Body Donation Program (BBDP), and Apolipoprotein E4 (APOE4) Gene Dose Program

**Emily Edmonds (Co-I)** 09/2024 – 08/2026
NIH via University of California, San Diego $138,259 Total Project
R01 (Grilli)

**Emily Edmonds (Project PI)** 07/01/2023 – 06/30/2024
Arizona DHS via Arizona Alzheimer's Consortium $70,000 Total Project
Data-driven Neuropsychological Diagnoses in the Arizona Alzheimer's Consortium

**Eric Reiman (Co-I)** 10/01/2020-03/31/2026
NIH/NIA $27,473,070
R01 AG069453 (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 (Zlokovic/Toga)
Vascular Contributions to Dementia and Genetic Risk Factors for Alzheimer's Disease

**Eric Reiman (Co-I)** 03/01/2020-06/30/2025
Alzheimer's Association via USC $402,553
VCID-17-209279 (Zlokovic/Toga)
Vascular Contributions to Dementia and Amyloid and Tau Lesions in APOE4 Carriers (VCID)

**Eric Reiman (Co-I)** 07/01/2021 – 05/31/2026
NIH/NIA via University of Washington $133,900
U24AG072122 (Kukull)
National Alzheimer's Coordinating Center

**Eric Reiman (Co-I)** 09/01/2017-05/31/2023
NIH/NIA via Massachusetts General Hospital $208,812
R01AG054671 (Quiroz)
Relationship between tau pathology and cognitive impairment in autosomal dominant Alzheimer's disease

**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)** 09/22/2017-04/30/2024
NIH/NIMHH via University of Colorado Denver $571,665
U54MD000507 (Manson/Buchwald)
American Indian and Alaska Native Health Disparities

**Eric Reiman (Co-I)** 08/01/2022-07/31/2025
NIH/NIA $2,282,378
RF1AG0733424 (Su)
Tracer harmonization for amyloid and tau PET imaging using statistical and deep learning techniques

**Eric Reiman (Co-I)** 05/2021-05/2025
NIH/NIA via University of Arizona $881,958
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)** 09/01/2020-08/31/2024
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)** 04/01/2017-03/31/2024
NIH/NIA $14,893,051
R01AG055444 (Reiman/Tariot/Lopera)
Alzheimer's Prevention Initiative ADAD Colombia Trial

**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)** 12/15/2015-11/30/2023
NIH/NINDS via Boston University/Mayo Clinic $281,796
U01NS093334 (Stern/Cummings/Reiman/Shenton)
Chronic Traumatic Encephalopathy: Detection, Diagnosis, Course and Risk Factors

**Eric Reiman (PI)** 04/01/2018-03/31/2024
NIH via University of Arizona $51,499,175
OT2 OD026549 (Moreno/Reiman/Theodorou)
University of Arizona-Banner Health All of Us Research Program

**Eric Reiman (PI)** 09/01/2007-06/30/2023
NOMIS Foundation (Reiman/Liang/Beach/Readhead/Dudley) $5,000,000
NOMIS Foundation via Banner Alzheimer's Foundation
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 (PI)** 09/01/2021-06/30/2026
NIH/NIA via ASU $15,077,717
P30AG072980
Arizona Alzheimer's Disease Research Center

**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

**Ganesh Gopalakrishna (Project PI)** 07/01/2023-06/30/2024
State of Arizona DHS via Arizona Alzheimer's Consortium $30,000
AI-Based Memory Problem Navigator

**Hillary Protas (Co-I)** 07/01/2021 – 01/31/2024
NIH/NIA via Johns Hopkins University $27,890
R01AG059390 (Smith)
Longitudinal Molecular Imaging of Neuropathology and Serotonin in Mild Cognitive Impairment

**Hillary Protas (Co-I)** 08/01/2022-07/30/2025
NIH/NIA R01AG073424 (Su) $2,282,378
Tracer harmonization for amyloid and tau PET imaging using statistical and deep learning techniques

**Hillary Protas (Project Co-I)** 07/01/2023-06/30/24
State of Arizona DHS via Arizona Alzheimer's Consortium $100,000
Statistical and Neuroimaging Data Science Core Resources Serving the Consortium Members

**Hillary Protas (Project Co-I)** 07/01/2023-06/30/24
State of Arizona DHS via Arizona Alzheimer's Consortium $110,000
Advanced Imaging and Machine Learning in Alzheimer's Research

**Jeremy Pruzin (Co-I)** 07/2023-06/2025
NIH via ASU 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

**Jeremy Pruzin (Co-I)** 05/01/2022-03/31/2027
NIH via University of Southern California $1,015,500
P01AG052350 (Zlokovic/Toga)
Vascular Contributions to Dementia and Genetic Risk Factors for Alzheimer's Disease

**Jeremy Pruzin (Project Co-I)** 07/01/2023-06/30/2024
Arizona DHS via Arizona Alzheimer's Consortium $70,000
Returning Results to Research Participants

**Jessica Langbaum (Co-I)** 04/01/2017-03/31/2024
NIH/NIA R01AG055444 (Reiman/Tariot/Lopera) $14,893,051
Alzheimer's Prevention Initiative ADAD Colombia Trial

**Jessica Langbaum (Co-I)** 09/30/2018-05/31/2025
NIH/NIA via USC R01AG061848 (Aisen/Johnson/Sperling) $750,000
Combination anti-amyloid therapy for preclinical Alzheimer's Disease

**Jessica Langbaum (Co-I)** 11/01/2021-10/31/2024
Alzheimer's Association via University of Southern California $150,000
SG-22-87715-AHEAD (Raman)
ACTC AHEAD Alzheimer's Association Proposal: Diverse Recruitment Component

**Jessica Langbaum (Collaborator)** 07/2021-06/2027
Eli Lilly and Company $4,116,286
TRAILBLAZER-ALZ3

**Jessica Langbaum (Core Co-Leader; Co-I)** 09/01/2021-06/30/2026
NIH/NIA via ASU $15,077,717
P30AG072980
Arizona Alzheimer's Disease Research Center

**Jessica Langbaum (PI)** 09/01/2018- 11/30/2025
NIH/NIA $32,005,950
R01AG058468 (Reiman/Aisen/Johnson/Langbaum/Sperling/ Tariot)
API A4 Alzheimer's Prevention Trial

**Jessica Langbaum (PI)** 09/01/2019-06/30/2025
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)** 09/15/2020-06/30/2025
NIH/NIA R01 AG063954-03S1 (Langbaum/Bleakley) $775,898
Establishing the science behind Alzheimer's recruitment registries: opportunities for increasing diversity and accelerating enrollment into trials (Admin Supplement)

**Jessica Langbaum (PI)** 07/01/2020-03/31/2026
NIH/NIA R01AG069453 (Reiman/Woodruff/Su/Langbaum) $27,473,070
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)** 07/01/2023-06/30/2024
Arizona DHS via Arizona Alzheimer's Consortium $365,000
Scientific Support to Enhance the Alzheimer's Prevention Initiative

**Jessica Langbaum (Project PI)** 07/01/2023-06/30/2024
Arizona DHS via Arizona Alzheimer's Consortium $20,000
Alzheimer's Prevention Registry and its GeneMatch Program

**Jessica Langbaum (Project PI)** 07/01/2023-06/30/2024
Arizona DHS via Arizona Alzheimer's Consortium $70,000
Returning Results to Research Participants

**Michael Malek-Ahmadi (Co-I)** 09/05/2021-06/30/2026
NIH/NIA via ASU P30AG072980 (Reiman) $15,077,717
Arizona Alzheimer's Disease Research Center – Data Management & Statistics Core

**Michael Malek-Ahmadi (Co-I)** 07/01/2023-06/30/24
State of Arizona DHS via Arizona Alzheimer's Consortium $110,000
Advanced Imaging and Machine Learning in Alzheimer's Research

**Michael Malek-Ahmadi (Co-I)** 04/01/2023-03/31/2026
NIH via Dignity Health RF1AG081286 (Perez) $85,869
Default Mode Network Dysfunction in Down Syndrome

**Michael Malek-Ahmadi (Core Leader; Co-I)** 04/01/2020-03/31/2025
NIH/NIA via Dignity Health P01AG014449 (Mufson) $793,090
Neurobiology of Mild Cognitive Impairment in the Elderly

**Michael Malek-Ahmadi (PI)** 06/01/2023-03/31/2025
NIH/NIA R03AG077270 $178,520
Cardiovascular Genotype and APOE ε4 Carrier Status Interaction Effects on Amyloid Load in Pre-Clinical Alzheimer's Disease

**Michael Malek-Ahmadi (Project Co-I)** 07/01/2023-06/30/24
State of Arizona DHS via Arizona Alzheimer's Consortium $100,000
Statistical and Neuroimaging Data Science Core Resources Serving the Consortium Members

**Michael Malek-Ahmadi (Project Co-I)** 07/01/2023-06/30/24
State of Arizona DHS via Arizona Alzheimer's Consortium $60,000
Enhancing Clinical and Biological Characterization of The Longevity Cohort Study: Global Staging and Biospecimen Banking

**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)** 09/2023-08/2028
NIH/NIA via USC U24AG057437 (Aisen) $354,696
Alzheimer's Clinical Trial Consortium

**Pierre Tariot (PI)** 04/01/2017-03/31/2024
NIH/NIA $14,893,051
R01AG055444 (Reiman/Tariot/Lopera)
Alzheimer's Prevention Initiative ADAD Colombia Trial

**Robert Alexander (Co-I)** 04/2017-03/2024
NIH/NIA R01AG055444 (Reiman/Tariot/Lopera) $14,893,051
Alzheimer's Prevention Initiative ADAD Colombia Trial

**Robert Alexander (Co-I)** 08/2022-01/2027
NIH/NIA via Institute for Molecular Medicine $95,630
(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 (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 (PI)** 09/2018-11/2025
NIH/NIA $32,005,950
R01AG058468 (Reiman/Aisen/Alexander/Langbaum/Sperling)
API / A4 Alzheimer's Prevention Trial

**Steven Rapcsak (Co-I)** 05/01/2022 – 04/30/2024
NIH via University of Arizona $415,614 Total Project
R21AG077153 (Chou)
Interleaved TMS-fMRI for Hippocampal Stimulation: Modeling Dose-Response Relationship in Amnestic Mild Cognitive Impairment

**Steven Rapcsak (Co-I)** 05/01/2020 – 01/31/2025
NIH via University of Arizona $3,468,515 Total Project
R01AG062453 (Chou)
Enhancement of Hippocampal Plasticity Using Repetitive Transcranial Magnetic Stimulation

**Steven Rapcsak (Co-I)** 08/15/2022 – 04/30/2027
NIH via University of Arizona $46,485 Total Project
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)** 12/2022 – 06/2026
NIH via University of Arizona $83,318 Total Project
R01EB032674 (Saranathan)
Next-Generation Thalamic Nuclei Visualization and Segmentation Methods

**Steven Rapcsak (Site PI)** 09/2021-06/2026
NIH/NIA via Arizona State University $911,967 Total Project
P30AG072980 (Reiman)
Arizona Alzheimer's Disease Research Center

**Steven Rapcsak (Site PI)** 07/2023-06/2024
Arizona DHS via Arizona Alzheimer's Consortium $140,000 Total Project
Hispanic Outreach, Recruitment and Retention Program
Alzheimer's Consortium

**Valentina Ghisays (Co-I)** 08/01/2022-07/30/2025
NIH/NIA RF1AG073424 (Su) $2,282,378
Tracer harmonization for amyloid and tau PET imaging using statistical and deep learning techniques

**Valentina Ghisays (Co-I)** 09/30/2020-03/31/2026
NIH/NIA R01AG069453 (Reiman) $27,473,070
APOE in the Predisposition to, Protection from and Prevention of Alzheimer's Disease

**Valentina Ghisays (Co-I)** 07/01/2023-06/30/2024
State of Arizona via Arizona Alzheimer's Research Consortium $110,000
Advanced Imaging and Data Analysis in Alzheimer's Research

**Valentina Ghisays (Co-I)** 07/01/2023 – 06/30/2024
State of Arizona via Arizona Alzheimer's Research Consortium $100,000
Statistical and Neuroimaging Data Science Core Resources Serving the Consortium Members

**Valentina Ghisays (Co-I)** 06/01/2023-03/31/2025
NIH/NIA R03AG077270 $178,520
Cardiovascular Genotype and APOE ε4 Carrier Status Interaction Effects on Amyloid Load in Pre-Clinical Alzheimer's Disease

**Valentina Ghisays (Collaborator)** 03/2023 - Present
F. Hoffman-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 R07269162 following oral administration in presymptomatic PSEN1 E280A mutation carriers and in non-carriers from the same kindred (BP44161)

**Valentina Ghisays (Project PI)** 09/2023-08/2024
NIH via University of Arizona $30,000
Precision Medicine for All of Us Researchers Collective, Medicina de Precision: Colectivo de Investigadores Salud para Todos

**Valentina Ghisays (REC Scholar)** 07/2023-06/2024
NIH via ASU P30AG072980 (Reiman) $26,667
Alzheimer's Disease Research Center

**Yi Su (Co-I)** 06/01/2023 – 03/31/2024
NIH/NIA R03 AG077270 (Malek-Ahmadi) $178,520
Cardiovascular Genotype and APOE ε4 Carrier Status Interaction Effects on Amyloid Load in Pre-Clinical Alzheimer's Disease

**Yi Su (Co-I)** 04/15/2018-03/31/2024
NIH/NIA R01AG055444 (Reiman/Tariot/Lopera) $14,893,051
Alzheimer's Prevention Initiative ADAD Colombia Trial

**Yi Su (Co-I)** 09/01/2018-11/30/2025
NIH/NIA R01AG058468 $32,005,950
(Reiman/Aisen/Johnson/Langbaum/Sperling/Tariot)
API / A4 Alzheimer's Prevention Trial

**Yi Su (Co-I)** 05/01/2019-04/30/2024
U54 MD000507 (Manson) $208,030
NIH/NIMHH via University of Colorado Denver
American Indian and Alaska Native Health Disparities

**Yi Su (Co-I)** 01/01/2021-08/31/2023
NIH via MS Technologies R42AG053149 (Lure) $241,309
Multi-Modality Image Data Fusion and Machine Learning Approaches for Personalized Diagnostics and Prognostics of MCI due to AD

**Yi Su (Co-I)** 12/01/2020-11/30/2023
NIH/NIA via Boston University U01NS093334 (Stern) $112,381
Chronic Traumatic Encephalopathy: Detection, Diagnosis, Course, and Risk Factors

**Yi Su (Co-I)** 07/2023-06/2025
Gates Ventures LLC $452,041
Integrated Expandable Platform to Facilitate Neuroscience Research

**Yi Su (Co-I)** 07/2023-06/2025
NIH via ASU 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 Co-Leader)** 07/01/2021-06/30/2026
NIH/NIA via ASU P30AG072980 (Reiman) $4,984,211
Arizona Alzheimer's Disease Research Center – Biomarker Core

**Yi Su (PI)** 08/01/2022-07/30/2025
NIH/NIA RF1AG073424 (Su) $2,282,378
Tracer harmonization for amyloid and tau PET imaging using statistical and deep learning techniques

**Yi Su (PI)** 09/30/2020-03/31/2026
NIH/NIA R01AG069453 (Reiman) $27,473,070
APOE in the Predisposition to, Protection from and Prevention of Alzheimer's Disease

**Yi Su (Project PI)** 07/01/2023 – 06/30/2024
State of Arizona via Arizona Alzheimer's Research Consortium $100,000
Statistical and Neuroimaging Data Science Core Resources Serving the Consortium Members

**Yi Su (Project PI)** 07/01/2023-06/30/2024
State of Arizona via Arizona Alzheimer's Research Consortium $110,000
Advanced Imaging and Data Analysis in Alzheimer's Research

**Alireza Atri (Co-I)** 06/01/2022- 05/31/2025
NIH via Indiana University U01AG057195 (Apostolova) $125,035 Total Project
Early Onset AD Consortium-the LEAD Study (LEADS) Social Worker Funds

**Alireza Atri (Co-I)** 03/01/2021-02/28/2026
NIH/NIA via University of Wisconsin-Madison $264,852 Total Project
R01AG070883 (Bendlin/Kind)
The Neighborhoods Study: Contextual Disadvantage and Alzheimer's Disease and Related Dementias

**Alireza Atri (Co-PI)** 09/01/2022-09/01/2026
Foundation for the National Institutes of Health (Finnema) ~$3,000,000 Total Project
Pre- competitive Analytical Validation of SV2A PET as a Biomarker of Synaptic Density (From Imaging to Autopsy)

**Alireza Atri (Co-PI)** 09/01/2020-08/31/2024
Gates Ventures via Banner Alzheimer's Foundation (Reiman) $3,085,720 Total Project
Resources for the Diagnostic and Prognostic Validation of Blood-Based Biomarkers of Alzheimer's Disease, Parkinson's Disease and Related Disorders

**Alireza Atri (Core Co-Leader, Co-I; BSHRI Site PI)** 07/01/2021-06/30/2026
NIH via Arizona State University P30AG072980 (Reiman) $15,077,717 Total Project
Arizona Alzheimer's Disease Research Center

**Alireza Atri (Project Co-I)** 07/01/2023-06/30/2024
Arizona Alzheimer's Consortium via Arizona DHS (Choudhury) $56,250 Total Project
Trajectories of clinical symptoms and associations with pathology in Lewy body spectrum disorders

**Alireza Atri (Project PI)** 04/01/2022-08/31/2023
Alzheimer's Association via University of Southern California $150,000 Total Project
SG-22-877415-AHEAD (Raman)
CTC AHEAD Alzheimer's Association Proposal: Diverse Recruitment Component

**Alireza Atri (Project PI)** 07/01/2023-06/30/2024
Arizona DHS via Arizona Alzheimer's Consortium (Atri) $225,000 Total Project
Enhancing Clinical and Biological Characterization of The Longevity Cohort Study: Global Staging and Biospecimen Banking

**Alireza Atri (Project PI)** 07/01/2023-06/30/2024
Arizona DHS via Arizona Alzheimer's Consortium (Atri) $62,500 Total Project
Development, Validation and Implementation of Cognitive and Clinical Composites for the Arizona Study of Aging and Neurodegenerative Disorders/BBDP

**Alireza Atri (Project PI)** 07/01/2023-06/30/2024
Arizona DHS via Arizona Alzheimer's Consortium (Atri) $81,250 Total Project
Enhancement of Arizona Alzheimer's Consortium Resource Sharing and Recruitment

**Alireza Atri (Site PI)** 11/01/2021-10/31/2024
Washington University St. Louis NCT01760005 (Bateman) $258,104 Total Project
DIAN-TU-001: A Phase II/III Multicenter Randomized, Double-Blind, Placebo-Controlled Platform Trial of Potential Disease Modifying Therapies Utilizing Biomarker, Cognitive, and Clinical Endpoints in Dominantly Inherited Alzheimer's Disease (DIAN) - Gantenerumab Open Label Study (DIAN-TU-001 Gant OLEX)

**Alireza Atri (Site PI)** 09/15/2023-08/31/2028
NIH via University of Southern California U24AG057437 (Aisen) $1,809,775 Total Project
Alzheimer's Clinical Trial Consortium

**Alireza Atri (Site PI)** 05/01/2019-04/30/2024
NIH via University of Southern California R01AG053798 (Aisen) $80,000 Total Project
Global Alzheimer's Platform Trial-Ready Cohort for Preclinical/Prodromal Alzheimer's Disease

**Geidy Serrano (Co-I)** 08/15/2021-08/31/25
NIH/NINDS R01NS118669-01 (Beach) $3,195,450 Total Project
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 (Reiman) $4,984,211 Total Project
Arizona Alzheimer's Disease Research Center-Biomarker Core

**Geidy Serrano (Co-I)** 07/01/2023-06/30/2024
Arizona Alzheimer's Research Consortium (Atri) $165,000 Total Project
Enhancing Clinical and Biological Characterization of The Longevity Cohort Study: Global Staging and Biospecimen Banking

**Geidy Serrano (Co-PI)** 09/01/2020-08/31/2024
Gates Ventures via Banner Alzheimer's Foundation (Beach) $3,085,720 Total Project
Resources for the Diagnostic and Prognostic Validation of Blood-Based Biomarkers of Alzheimer's Disease, Parkinson's Disease and Related Disorders

**Geidy Serrano (Co-PI)** 02/01/2023-01/31/2025
Michael J Fox Foundation MJFF-022763 (Beach/Serrano) $622,388.05 Total Project
Alpha-synuclein aggregate presence in gastrointestinal tract relative to CNS in 200 neuropathologically-evaluated autopsy subjects

**Geidy Serrano (Co-PI)** 10/1/2023-09/30/2024
MJFF (Jaunmuktane) $97,936 Total Project
Planning grant for an international digital pathology resource from patients with Parkinson's disease and controls

**Geidy Serrano (Core Co-Leader; Co-I)** 09/05/2021-06/30/2026
NIH/NIA via ASU P30AG072980 (Reiman) $1,636,000 Total Project
Arizona Alzheimer's Disease Research Center-Neuropathology Core

**Geidy Serrano (Project PI)** 07/1/2023-06/30/2024
Arizona Alzheimer's Research Consortium (Serrano) $115,000 Total Project
Patient-based postmortem fibroblast banking for translational research

**Geidy Serrano (Project PI)** 07/01/2023-06/30/2024
Arizona Alzheimer's Research Consortium (Serrano) $190,000 Total Project
A Human Brain Single-Cell Suspension Resource

**Geidy Serrano (Site-PI)** 04/01/2021-03/31/2026
NIH/University of Arizona R01AG072643 (Barnes) $40,875 Total Project
NPTX2: Preserving memory circuits in normative aging and Alzheimer's Disease

**Geidy Serrano (Site-PI)** 12/01/2023-11/30/2028
NIH (Mukherjee) $106,596 Total Project
Novel Tau-Targeted Radiohalogenated Agents for Alzheimer's Disease

**Parichita Choudhury (Co-I)** 07/01/2021-06/30/2026
NIH via Arizona State University P30AG072980 (Reiman) $15,077,717 Total Project
Arizona Alzheimer's Disease Research Center

**Parichita Choudhury (Co-I)** 07/01/2023-06/30/2024
Arizona DHS via Arizona Alzheimer's Consortium (Atri) $81,250 Total Project
Enhancement of Arizona Alzheimer's Consortium Resource Sharing and Recruitment

**Parichita Choudhury (Co-I)** 09/15/2023-08/31/2028
NIH via University of Southern California U24AG057437 (Aisen) $1,809,775 Total Project
Alzheimer's Clinical Trial Consortium (estimated)

**Parichita Choudhury (Project PI)** 07/01/2023-06/30/2024
Arizona Alzheimer's Consortium via Arizona DHS (Choudhury) $56,250 Total Project
Trajectories of clinical symptoms and associations with pathology in Lewy body spectrum disorders

**Thomas Beach (Co-I)** 09/15/2020-08/31/2024
NIH via UCSB R01AG062479 (Kosik) $382,349 Total Project
The complex interaction between Alzheimer's drivers and aging

**Thomas Beach (Co-I)** 01/01/2024-09/30/2024
MJFF via Yale ASAP-000301(Scherzer) $102,920.57 Total Project
Parkinson5D: deconstructing proximal disease mechanisms across cells, space, and progression

**Thomas Beach (Co-I)** 06/01/2021-05/31/2025
NIH via University of Kentucky R01AG068331 (Ebbert) $201,471 Total Project
Using long-range technologies as a multi-omic approach to understand Alzheimer's disease in brain tissue

**Thomas Beach (Co-I)** 07/01/2021-06/30/2026
NIH/NIA via ASU 1P30AG072980-01 (Reiman) $4,984,211 Total Project
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 Total Project
R01AG070883 (Kind)
The Neighborhoods Study: Contextual Disadvantage and Alzheimer's Disease and Related Dementias

**Thomas Beach (Co-I)** 07/01/2023-06/30/2024
Arizona Alzheimer's Research Consortium (Reiman) $190,000 Total Project
A Human Brain Single-Cell Suspension Resource

**Thomas Beach (Co-I)** 09/01/2023 – 08/30/2024
NIH via Arizona Veterans Research and $14,509 Total Project
Education Foundation 1R56AG083570 - 01 (Migrino)
Understanding and reversing vascular aging-related dementia through medin signaling

**Thomas Beach (Co-I)** 02/01/2024-01/31/2028
NIH via BU R01HL171499 (Mizgerd) $96,700 Total Project
Fibrin in the Infected Lung

**Thomas Beach (Consultant)** 05/17/2021-05/16/2025
Phoenix VA Health Care System 2I01BX003767-05 (Migrino) $60,000 Total Project
Discovering novel mechanisms for aging-related dementia: probing medin and abeta vasculopathy

**Thomas Beach (Co-PI)** 09/01/2020-08/31/2024
Gates Ventures via Banner Alzheimer's Foundation (Reiman) $3,085,720 Total Project
Resources for the Diagnostic and Prognostic Validation of Blood-Based Biomarkers of Alzheimer's Disease, Parkinson's Disease and Related Disorders

**Thomas Beach (Co-PI)** 10/1/2023-09/30/2024
MJFF via UCL (Jaunmuktane) $97,936 Total Project
Planning grant for an international digital pathology resource from patients with Parkinson's disease and controls

**Thomas Beach (Co-PI)** 02/01/2023-01/31/2025
Michael J Fox Foundation MJFF-022763 (Beach/Serrano) $622,388.05 Total Project
Alpha-synuclein aggregate presence in gastrointestinal tract relative to CNS in 200 neuropathologically-evaluated autopsy subjects

**Thomas Beach (Core Leader)** 09/05/2021-06/30/2026
NIH/NIA via ASU P30AG072980 (Reiman) $1,636,000 Total Project
Arizona Alzheimer's Disease Research Center-Neuropathology Core

**Thomas Beach (PI)** 07/01/2021-06/30/2025
NIH/NINDS R01NS118669 (Beach) $3,195,450 Total Project
Blinded Comparison of Different Alpha-Synuclein Seeding Assays as Cutaneous Biomarkers of Lewy Body Dementias

**Thomas Beach (PI)** 06/23/2016-11/01/2024
MJFF-020674 (Beach) $606,060 Total Project
Systemic Synuclein Sampling Study

**Thomas Beach (Site PI)** 08/15/2021-7/30/2026
NIH via UCSF Gladstone P01AG073082 (Mucke) $200,575 Total Project
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 Total Project
Sex Differences in the Clinical Expression of Alzheimer's Disease Neuropathology and Their Underlying Biological Mechanisms

**Thomas Beach (Site PI)** 12/01/2021-11/30/2026
NIH via Binghamton University R01NS122226 (Bishop) $54,597 Total Project
Interrogating maladaptive serotonin raphe-striatal plasticity in L-DOPA-induced dyskinesia

**Thomas Beach (Site PI)** 07/01/2021-6/30/2024
ABRC via Mayo Clinic Arizona CTR056041 (Adler) $182,963 Total Project
Submandibular gland needle core biopsy as a tissue biomarker the diagnosis of Parkinson's disease and the monitoring of disease progression

**Thomas Beach (Site PI)** 04/01/2022-03/31/2027
NIH via Stanford University R01AI162850 (Mizgerd) $203,196 Total Project
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 Total Project
Skin biomarkers for diagnosing and characterizing AD and ADRD

**Thomas Beach (Site PI)** 06/01/2023-02/2025
NIH via UAB 1R01AG082352-01(Chen) $111,699 Total Project
Peripheral Biomarkers for Early Diagnosis of Mixed Pathologies in AD/ADRD

**Thomas Beach (Site-PI)** 04/01/2023 – 03/31/2028
NIH via UCSD R01AG079280-01 (Frank) $143,353 Total Project
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 UH 1R01CA276733-01 (Wu) $68,713 Total Project
Uncovering causal protein markers to characterize prostate cancer etiology and improve risk prediction in Africans and Europeans

**Thomas Beach (Site-PI)** 08/01/2022-07/30/2024
NIH via TGEN 1R21NS128550-01 (Sattler) $31,947 Total Project
Transcriptomic assessment of pathology in PD with dementia and dementia with Lewy Bodies using iPSC neurons and brain tissue of the same individuals

## Pending Grants

**David Medina (PI)**
LifeArc
Repurposing FTO inhibitors for the treatment of ALS

**Rita Sattler (PI)** 09/01/24-08/31/26
NIH/NINDS R21 $376,938
Contribution of astrocytic SPARCL1 to cortical synaptic dysfunction in C9orf72 FTD/ALS

**Rita Sattler (Multi-PI)** 09/01/24-08/31/26
NIH/NINDS R21 $433,795
Cross validation of gene expression changes in C9orf72 FTD using Drosophila and human model systems.

**Rita Sattler (Multi-PI)** 07/01/24-06/30/26
Target ALS Consortium $1,000,000
Mechanisms of glial-associated TDP-43 pathology and contributions to neurodegeneration

**Ashley Stokes (Co-PI) (Manfredsson, Bishop, Tseng)** 10/01/2024 – 09/30/2028
Department of Defense, CDMRP $655,380 Total Project
Maladaptive 5-HT raphe-corticolimbic plasticity underlying the development of non-motor behavioral symptoms in Parkinson's Disease

**Ashley Stokes (PI)** 07/01/2024 – 06/30/2025
AZ Alzheimer's Consortium / Barrow Neurological Foundation $136,800 Total Project
Establishing the neuropathological underpinnings of altered functional connectivity using preclinical models of AD

**Ann Revill (PI)** 07/01/2024-06/30/2025
AZ Dept of Health Services-Arizona Alzheimer's Consortium $60,000 Total Project
FY25 Developmental Project
Physiological and anatomical hallmarks associated with intermittent hypoxia and aging – insights into respiratory dysfunctions associated with Alzheimer's disease

**Ann Revill (PI)** 07/01/2024-06/30/2027
R15HL175526 $421,800 Total Project
NIH R15 REAP
Effects of chronic intermittent hypoxia on cholinergic modulation at hypoglossal motoneurons

**Elizabeth Hull (PI) and Kathryn Leyva (Co-I)** 06/01/2025-05/31/2028
AZ240274 $1,000,000 Total Project
Department of Defense
Elucidating the mechanistic links between lysosome function and biological activity of progranulin to reduce the pro-inflammatory response to brain injury and neurodegeneration

**Elizabeth Hull (PI) and Kathryn Leyva (Co-I)** 09/01/2024-08/31/2027
R15AG091200 $421,800 Total Project
NIH R15 REAP
Elucidating a mechanistic link between progranulin and lysosomal function in the pro-inflammatory response to guide development of therapeutics effective in early intervention in Alzheimer's disease

**Elizabeth Hull & Kathryn Leyva** Funded 7/1/24-6/30/25
Midwestern Arizona Alzheimer Consortium $24,930
The role of progranulin in the inflammatory response in Alzheimer disease

**Greg Caporaso (PI)** 07/2025 – 06/2030
NIH $4,573,836 Total Award
Advancing cancer research with the QIIME 2 microbiome data science platform.

**Greg Caporaso (PI)** 01/2025 – 12/2027
NSF $2,995,847 Total Award
TRAILBLAZER: Harnessing Microbiomes to Sustainably Manage and Upcycle Human Excrement

## CURRENT & PENDING GRANTS

**Greg Caporaso (co-I)** 09/2024 – 08/2029
U54CA143925 (Ingram) $6,362,552 Total Project
NIH NCI
The Partnership for Native American Cancer Prevention

**Emily Cope (PI)** 07/01/2024-06/30/2025
Pending (Cope) $150,000 Total Project
Arizona Alzheimer's Consortium Alzheimer's /AZDHS
Arizona Statewide Alzheimer's Research

**Emily Cope (Research Mentor)** 05/2025-04/2030
T32 - PAR- 24-037. (de Heer) $2,104,903 Total Project
G-RISE at Northern Arizona University

**PI:Traustadóttir** Submitted June 2024
Arnold and Mabel Beckman Foundation $167,825
Beckman Scholars Program

**McCarthy, M; Cerino, E; McCoy, M (Co-PIs)** 07/01/2024-06/30/2025
Arizona Alzheimer's Consortium Alzheimer's /AZDHS $160,000 Total Project
Development of Tailored Technologies and Resources to Identify and Support Rural Caregiver-Receiver Dyads with Mild Cognitive Impairment Due to Alzheimer's Disease – Year 2

**Michael McCarthy (Co-I)** 09/01/2024-08/31/2027
U54CA143925 (Hammer/Godfrey) $180,000 Total Project
Partnership for Native American Cancer Prevention

**Michael McCarthy (Co-I, Site PI)** 12/01/2024-11/30/2029
R01CA28733 (Lyons) $3,916,603 Total Project
We are in this Together: The Role of Dyadic Processes in optimizing Health in Family Care Dyads living with Lung Cancer

**Michael McCarthy (Research Mentor)** 05/2025-04/2030
T32 - PAR- 24-037. (de Heer) $2,104,903 Total Project
G-RISE at Northern Arizona University

**Eric Cerino (Research Mentor)** 05/2025-04/2030
T32 - PAR- 24-037. (de Heer) $2,104,903 Total Project
G-RISE at Northern Arizona University

**Eric Cerino (Co-I)** 12/01/2024 – 11/30/2029
NIA – R01 – PA-20-185 (Charles, Rush) $2,000,000 Total Project
Linking Daily Dynamics of Social Connection to Physical and Cognitive Functioning

**Matthew Huentelman (Co-I)** 07/01/2024 – 06/30/2026
NA (Madhavan) $151,309 Total Project
NSF via University of Arizona
Neural Stem Cell Mechanisms of Resilience across the lifespan

**Matthew Huentelman (Co-I)** 08/01/2024 – 07/31/2029
R01 (Seidler) $103,727 Total Project
NIH via University of Florida
Neural Correlates of Cognitive-Motor Interactions in ADRD Gait

**Matthew Huentelman (Co-I)** 07/01/2024 – 06/30/2026
NA (Piras) $230,400 Total Project
Arizona Alzheimer's Research Center via Banner Health
Development of Alzheimer's Disease forebrain neuronal organoid models

**Matthew Huentelman (Co-I)** 07/01/2024 – 06/30/2026
R21 (Huseby) $142,770 Total Project
NIH via Arizona State University
Investigating mechanisms of cell-type vulnerability in Alzheimer's and other nuerodegenerative disease usign IPSC

**Matthew Huentelman (Co-I)** 07/01/2024 – 06/30/2027
NA (Shi) $442,998 Total Project
California's Institute for Regenerative Medicine via City of Hope
Human iPSC-based 2D and 3D models for studying rare disease-causing mutations on CK2 actions

**Matthew Huentelman (Co-I)** 04/01/2024 – 03/31/2025
NA (Windsor) $ 94,951 Total Project
American Kennel Club Canine Health Foundation via Ethos Discovery
Stem cell Therapy for Early Encephalitis in Pugs (STEEP): Opportunities for enhancing our understanding of Pug Dog Encephalitis Pathogenesis

**Matthew Huentelman (Co-I)** 09/01/2024 – 08/31/2029
R01 (Chong) $ 325,745 Total Project
NIH via Mayo Clinic, AZ
A comprehensive investigation into the complex relationship between migraine and major cardiovascular/cerebrovascular events (MACE): a multimodal machine-learning

**Matthew Huentelman (Co-I)** 12/01/2024 – 11/30/2028
R01 (Schaefer) $234,502 Total Project
NIH via Arizona State University
Developing a performance-based measure of daily function as an equitable approach to screening Hispanic/Latino older adults for Alzheimer's disease risk

**Matthew Huentelman (Co-I)** 11/01/2024 – 10/31/2028
NA (Shi) $1,441,676 Total Project
California's Institute for Regenerative Medicine via City of Hope
Modeling ASD and associated neurodevelopmental disorders using human iPSC-based 2D and 3D models

**Matthew Huentelman (Co-I)** 09/01/2025-08/31/2028
R01 (Velazquez) $610,794 Total Project
NIH via Arizona State University
Interrogating the protective effects of neuronal Rbbp7 against amyloidosis, tau acetylation, and neuroinflammation

**Raffaella Soldi (Co-I)** 09/2024-08/2026
NIH R41CA---- (Montesinos & Sharma) $2,050,000 Total Project
Development of a Personalized Neoantigen Vaccine for Enhanced Colon Cancer Immunotherapy: A Collaborative Approach Leveraging Advanced Genomic Insights and Immunological Responses

**Sunil Sharma (PI)** 09/2024-08/2026
NIH R41CA---- (Montesinos & Sharma) $2,050,000 Total Project
Development of a Personalized Neoantigen Vaccine for Enhanced Colon Cancer Immunotherapy: A Collaborative Approach Leveraging Advanced Genomic Insights and Immunological Responses

**Jonathan Lifshitz (PI)** 07/01/2023 – 06/30/2028
NIH/NICHD R01 HD110860-01A $3,837,490 Total Project
Gravida traumatic brain injury (TBI) impacts neurobehavioral and neurocircuitry phenotypes of the offspring

**Jonathan Lifshitz (PI)** 04/01/2022 – 03/31/2026
VA Merit I01 BX005956 $1,200,000 Total Project
U.S. Dept. of Veterans Affairs
Analytical Modeling of Acquired Neurological Injury with Rich Experimental Data Sets

**Jonathan Lifshitz (PI)** 07/01/2024 – 06/30/2027
Department of Defense $1,171,260 Total Project
VCR – Virtual cognitive rehabilitation using a virtual reality spatial navigation application for Veterans with a history of TBI

**Ying-hui Chou (MPI) and Nan-kuei Chen (MPI)** 07/2024-06/2026
NIH R21NS137573 $437,520 Total Award
Investigating electromagnetic field-based neuromodulation of slow-wave brain activity and glymphatic system

**Ying-hui Chou (MPI) and William Killgore (MPI)** 09/2024-08/2027
DoD $3,069,903 Total Award
Effectiveness of Transcranial Magnetic Stimulation of the Default Mode Network to Improve Sleep

**Ying-hui Chou (PI)** 07/2024-06/2029
NIH R01AG089910 $3,755,154 Total Award
Uncovering the Hidden Signs of Alzheimer's Disease: Advancing Assessments of Hyperexcitability, Cholinergic Dysfunction, and Impaired Plasticity Potential in Preclinical and Prodromal Stages

**Ying-hui Chou (MPI) and Mark H Sundman (MPI)** 12/2024-11/2026
NIH R03AG090765 $307,000 Total Award
Unlocking Metabolic Insights with Transcranial Magnetic Stimulation: Exploring a Novel Assay of Glycolytic Function in the Alzheimer's Disease Continuum

**Stephen Cowen (MPI)** 04/01/2025-03/31/2030
NIH R25 (R25AG092294) $1,049,340 Total Project
Teacher Teams Enhancing AD/ADRD Diverse Mentorship/Research Education in Arizona (TEAMAz) (Role: MPI, PI: Marlys Witte)

**Stephen Cowen (Co-I)** 12/01/2024-11/30/2029
NIH R01 (1R01NS136226) $3,215,500 Total Project
Uncovering Early Parkinson's Mechanisms Via A-Synuclein Driven
Vocal Dysfunction. (Role: Co-Investigator, PI: Julie Miller)

**Meredith Hay (PI)** 02/01/2025-01/31/2029
NIA UG3/UH3 $24,708,853
University of Arizona
"PNA5 For Treatment of Vascular Cognitive Impairment and Dementia (VCID) and Alzheimer's disease related dementias (ADRD): A Phase 1a/b Safety and Tolerability Study."

**Elizabeth Hutchinson (PI)** 04/01/2024-3/31/2026
NIH R21 AG091243 (Hutchinson) $407,972 Total Project
Radiologic-pathologic correspondence of diffusion MRI markers for the rod microglial response following traumatic brain injury

**Maggie O'Haire (PI) and Andrews-Hanna and Grilli (Co-Is)**
TBD $528,153 (requested)
WALTHAM Centre for Pet Nutrition

**Arne Ekstrom (PI) and Andrews-Hanna (Co-I)** 04/01/2024-03/31/2029
R01NS076856 $3,807,375 (requested)
NIH/NINDS

**Lee Ryan (Co-I)** 07/01/2024-06/30/2025
(Matijevic) $33,000 Total Project
Arizona Department of Health Services, AAC
Episodic and semantic detail generation across the adult lifespan

**Justin Snider (PI)** 04/01/2025-05/01/2027
Grants.govTracking # GRANT14185581 $306,547 Total Project
The Role of Deoxysphingolipids in Alzheimer's Disease

**Judith Su (PI)** 09/01/2024-02/28/2026
AIM Photonics $1,150,000 Total Project
FLOWER PETAL: Frequency locked optical whispering evanescent resonator for process evaluation and transient analytical logging

**Judith Su (PI)** 08/01/2024-07/31/2027
DARPA YFA $1,000,000 Total Project
Rapid discovery of effective drugs to block hazardous drug exposure through virtual screening and experimental validation

**Judith Su (PI)** 04/15/2024-04/14/2027
U.S. Army Combat Capabilities Development Command (DEVCOM) Chemical Biological Center (CBC) $2,075,000 Total Project
FORWARD: FLOWER-based optical resonators for widely applicable reagent detection

**Fei Yin (Subcontract PI)** 07/01/2024-06/30/2029
TBD (Selleck) $1,138,020 Subaward
NIH/NIA via Penn State University
Heparan sulfate proteoglycan regulation of autophagy, mitochondrial function and lipid metabolism in Alzheimer's Disease: A potential target for blocking neurodegeneration

**Fei Yin (Subcontract PI)** 12/01/2024-11/30/2029
TBD (Gu) $153,000 Subaward
NIH/NIA via ASU
Microplastics x ApoE4 x High-Fat Diet Interaction, Brain Aging, Microbial Indoles-AhR Signaling

**Zhou (PI)**
Zhou-CX-24-001
Veteran Affairs Administration
Role of Carotid Disease in Cognitive Impairment and Dementia

**Locke, Dona (Co-I) & Dumitrascu, Oana** Earliest start date: April 2025
R03AG093372-01 (Nina Sharp, ASU) $200,000 Total
Exploring the effectiveness and feasibility of an ambient bright light intervention to improve sleep and cognition in patients with mild cognitive impairment

**Locke, Dona (Co-I)** 10/1/2024-3/31/2026
Agewell: 2024 Age Tech Advance: Healthy Aging Research Program (Neil Thomas, PI) $150,000 Total
Electronic Memory Support System (eMSS): An Innovative Digital Tool for Care of Older Adults

**Locke, Dona (mentor)** Earliest start date: April 2025
NIH F32 HL176010-01
National Research Service Award (NRSA) Postdoctoral Fellowship Award
(Stacy Al-Saleh, PhD, Mayo Clinic)
The Feasibility of Measuring Sleep Health and Cognitive Functioning in Adult Heart Transplant Recipients

**Cheryl Conrad (Co-I)** 07/05/2024 – 07/04/2029
FP39771 Pentowski, (PI) $209,260 Total Award
University of New Mexico via NIH
The role of ventral hippocampal CRF1 receptors in regulating neuropsychiatric symptoms and neuropathology in a rat transgenic model of Alzheimer's disease

**Cheryl Conrad (Co-I)** 04/01/2025 – 03/31/2030
FP42971, Thomas (PI) $361,626 Total Award
University of Arizona via NIH
Mechanisms of HPA Axis Dysregulation and Amygdala Circuit Function Post-TBI

**David W. Coon (Co-I)**
Submitted to NIA (Fang Yu, PI) $4.39M
A Mechanistic SMART Trial of Precision Aerobic Exercise to Optimize Aerobic-Fitness, Biomarker, and Cognitive Responses in Alzheimer's Disease and Related Dementias.

**David W. Coon (Co-I)**
Submitted to NINR (Julie Fleury, PI) $2.25M
HOME: A Behavioral Clinical Trial to Promote Well-Being and Feelings of Safety among Older ADRD Caregivers.

**A. Peckham & M. Guest (Co-PI)** 01/01/2025-12/31/2028
Department of Defense, under review $999,726
CARE-MAPS: Identifying network compositions to support caregiver resilience for Alzheimer's disease and related dementias

**Candace Lewis (PI)** 9/1/2024 – 8/31/2029
1DP2MH140150, Lewis $1.5M
National Institutes of Health (NIH)
Individually Measured Endophenotypes to Advance Computational Translation in Mental Health

**Eleni Panagiotou (co-PI)** 09/01/2024-08/31/2027
NSF 2424880 $361,062 Total Project
Collaborative research: Identifying topologies for harnessing enzyme activity

**Eleni Panagiotou (co-PI)** 10/01/2024-09/30/2027
Department of Education $672,612 Total Project
GAANN Fellowships in the Mathematical Sciences at Arizona State University

**Heather Ross, PI** 12/01/2024 – 11/30/2026
FP00041135; PI: Ross $157,000
HHS: National Institutes of Health (NIH)
Tailored Multi-Stakeholder Feedback for Dementia & Mild Cognitive Impairment Screening in Older Adults Experiencing Homelessness

**Heather Ross, PI** 04/01/2025 – 03/31/2030
FP00043231, PI: Ross $3,007,523
HHS: National Institutes of Health (NIH)
Dis/Connected Systems of Care for People Experiencing Homelessness

**Heather Ross, PI; Diana Bowman, Co-PI** 10/01/2024 – 09/30/2026
National Science Foundation (NSF) $300,000
ReDDDoT Phase 1: Planning: Technology Design for Older Adults Experiencing Homelessness

**Heather Ross, Subaward PI** 10/01/2024 – 09/30/2027
FP00042650, PI: Taylor (City of Phoenix) $828,057
Department of Justice, Bureau of Justice Assistance (BJA) Minding the Gaps

**Heather Ross, PI** 01/01/2025 – 12/31/2026
FP00042531, PI: Ross $499,774
Department of Justice, National Institute of Justice (NIJ)
Beyond the Badge: Evaluating a Suite of Alternative Responses in Phoenix

**Heather Ross, PI; Diana Bowman, Co-PI** 10/01/2024 – 09/30/2026
FP00042976, PI: Ross $495,762
Department of Justice: Community-Oriented Policing Services (COPS) Community-Based Dementia Screening for Older Adults by Police Officers

**Sydney Schaefer (PI)** 12/01/2024 - 11/30/2029
R01AG091339-01 $2,598,804
National Institutes of Health
Developing a performance-based measure of daily function as an equitable approach to screening Hispanic/Latino older adults for Alzheimer's disease risk

**Sydney Schaefer (Co-I)** 4/1/2025-3/31/2030
1R01AG092583-01 (PI: Jessica Verpeut) $2,573,707
National Institutes of Health
Mapping Alzheimer's disease progression in preclinical models by quantifying relationships between brain microstructure, neural activity, and behavior

**Sydney Schaefer (PI)** 08/15/2024 – 08/14/2025
3R21AT012088-01A1W1 $105,298
National Institutes of Health
Administrative Supplement for Measuring Expectancy Effects of Transcranial Direct Current Stimulation on Motor Learning

**Nina Sharp (PI)** 04/01/2025 – 03/31/2027
R03 NIH/NIA (Sharp) $319,051 Total Project
Feasibility and efficacy of a personalized circadian-based lighting intervention to improve cognitive performance in patients with MCI

**Michael Sierks (PI)** 7/1/2024-6/30/2026
Project Number: FP00038790 $1,103,084
DOD-ARMY: Army Medical Research Acquisition Activity Developing a personalized blood based diagnostic assay for early detection of ALS

**Michael Sierks (PI)** 9/1/2024-8/31/2029
Project Number: FP00038241_Res1 $3,302,483
HHS: National Institutes of Health (NIH)
A novel therapeutic to promote neurogenesis and restore neuronal proteostasis after traumatic brain injury

**Michael Sierks (PI)** 7/1/2024-6/30/2026
Project Number: FP00040994 $228,873
Virtici / HHS: National Institutes of Health (NIH)
A Novel Neuroprotective TDP-43-Targeting Antibody for Treating Frontotemporal Dementia

**Michael Sierks (PI)** 11/1/2024-10/31/2029
Project Number: FP00041289 $2,171,038
HHS: National Institutes of Health (NIH)
Developing CAR-NK cells to target and clear diseased neurons in early AD

**Michael Sierks (PI)** 9/1/2024-8/31/2029
Project Number: FP00041312 $2,196,331
HHS: National Institutes of Health (NIH)
Development of biomarker panel for early detection of AD

**Sarah Stabenfeldt (MPI)** 09/01/2024-09/31/2026
1R21NS137527-01A1 (Stabenfeldt/Diehnelt) NIH/NINDS $423,900
Autoantibody profiling for TBI and neurodegenerative diagnostics

**Sarah Stabenfeldt (MPI)** 09/01/2024-08/31/2029
R01NS141186-01 (Acharya/Stabenfeldt) NIH/NINDS $3,767,880
Biomaterials for immunological defense from traumatic brain injury

**Sarah Stabenfeldt (MPI)** 07/01/2025-08/31/2030
T32GM154654-01 (Stabenfeldt/Brafman/Kusumi) NIH/NIGMS $4,289,839
RESTEP in AZ: Regenerative Engineering, Science, and Technology Education Program in Arizona

**Jessica Verpeut (PI)** 7/1/2024-6/30/2025
FP41742 - Award in process $30,000 Total Project
Arizona Alzheimer's Consortium (AAC Pilot Grant)
Mapping Alzheimer's disease progression in preclinical models by quantifying relationships between brain microstructure, neural activity, and behavior

**Jessica Verpeut (PI)** 4/1/2025-3/31/2030
R01 AG092583 $2,573,707 Total Project
NIH/NIA via Arizona State University
Multiscale Analysis of Alzheimer's Disease Pathogenesis: Measuring and Integrating Behavioral, Neural and Microstructural Changes Over Spatial and Temporal Scales

**Jessica Verpeut (PI)** 4/1/2025-3/31/2027
GRANT 14187361 $405,752 Total Project
NIH/NIDA via Arizona State University
Investigating the Neural and Behavioral Mechanisms of Social Withdrawal in Opioid Addiction and the Therapeutic Potential of Metformin

**Heather Bimonte-Nelson (PI); Verpeut: Co-I** 4/1/2025-3/31/2-30
R01 AG028084 $3,394,566 Total Project
NIH/NIA via Arizona State University
Variations in Hormones During Menopause: Effects on Cognitive and Brain Aging

**Yalin Wang (Project PI)** 7/1/2024-6/30/2025
Arizona Alzheimer's Consortium (Coon) State of Arizona $365,000
2024-2025 Arizona Alzheimer's Consortium (AAC)

**David Weidman (Project PI)** 07/01/2024-06/30/2025
Arizona DHS via Arizona Alzheimer's Consortium $66,667
Native American Outreach, Recruitment, and Retention Program

**Don Saner (Project PI)** 07/01/2024-06/30/2025
Arizona DHS via Arizona Alzheimer's Consortium $50,000
Automating Centralized Data Management Program for Arizona's Alzheimer's Disease and Related Studies

**Emily Edmonds (Co-I)** 07/01/2023 – 06/30/2028
NIH/NIA via UC San Diego (Thomas) $3,286,436
Heterogeneity of subtle cognitive decline phenotypes in community-dwelling older adults

**Emily Edmonds (Project PI)** 07/01/2023 – 06/30/2025
Arizona DHS via Arizona Alzheimer's Consortium $100,000
Characterizing Empirically Derived Cognitive Subgroups in the National Alzheimer's Coordinating Center

**Eric Reiman (PI)** 04/2024-03/2029
NIH/NIA R01AG086363 $76,637,320
Alzheimer's Prevention Initiative ADAD Colombia Trial

**Eric Reiman (PI)** 04/2025-03/2030
NIH/NIA via ASU R01AG092647 (Wu) $3,802,086
Multi-Scale Modeling of Aging and Alzheimer's Disease

**Eric Reiman (PI)** 04/2024-06/2029
NIH/NINDS via Boston University $15,538,237
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

**Ganesh Gopalakrishna (Project PI)** 07/01/2024-06/30/2025
Arizona DHS via Arizona Alzheimer's Consortium $22,222
AI-Based Memory Problem Navigator

**Jeremy Pruzin (Project PI)** 07/01/2024-06/30/2025
Arizona DHS via Arizona Alzheimer's Consortium $31,667
Impact of Dementia Untangled Podcast on Quality of Life and Caregiver Burden

**Jessica Langbaum (Co-I)** 04/2024 – 04/2029
NIH via Arizona State University (Tang) $116,008
Targeting Stress to Reduce Risk of ADRD through a Novel Body-Mind Intervention

**Jessica Langbaum (Co-I)** 04/2024 – 03/2030
NIH via Alzheimer's Association (Carillo/Raffi/Lynch) $696,603
Real World Data (RWD) in Alzheimer's Disease - Clinical Research Network Core

**Jessica Langbaum (PI)** 04/01/2024-03/31/2029
NIH/NIA $76,637,320
R01AG086363 (Alexander/Reiman/Langbaum/Lopera)
Alzheimer's Prevention Initiative ADAD Colombia Trial Program

**Jessica Langbaum (Project PI)** 07/01/2024-06/30/2025
Arizona DHS via Arizona Alzheimer's Consortium $365,000
Scientific Support to Enhance the Alzheimer's Prevention Initiative

**Jessica Langbaum (Project PI)** 07/01/2024-06/30/2025
Arizona DHS via Arizona Alzheimer's Consortium $50,000
Returning Results to Research Participants

**Jessica Langbaum (Project PI)** 07/01/2024-06/30/2025
Arizona DHS via Arizona Alzheimer's Consortium $22,222
Alzheimer's Prevention Registry and its GeneMatch Program

**Michael Malek-Ahmadi (Co-I)** 12/01/2024 – 11/30/2029
NIH via ASU (Schaefer) $69,276
Developing a performance-based measure of daily function as an equitable approach to screening Hispanic/Latino older adults for Alzheimer's disease risk

**Michael Malek-Ahmadi (PI)** 07/01/2024-06/30/2026
NIH 1R21AG088375-01 $440,892
Integrated Models of Subjective Cognitive Complaints in Cognitively Unimpaired Older Adults

**Michael Malek-Ahmadi (PI)** 04/01/2025 – 03/31/2030
NIH $54,470
Objective Assessment of Daily Function in Alzheimer's Disease: A Novel, Remote, Performance-Based Approach

**Michael Malek-Ahmadi (Project PI)** 07/01/2024-06/30/2025
Arizona DHS via Arizona Alzheimer's Consortium $100,000
Statistical and Neuroimaging Data Science Core Resources Serving the Consortium Members

**Pierre Tariot (Co-I)** 04/01/2024-03/31/2029
NIH/NIA $76,637,320
R01AG086363 (Alexander/Reiman/Langbaum/Lopera)
Alzheimer's Prevention Initiative ADAD Colombia Trial Program

**Robert Alexander (PI)** 04/2024-03/2029
NIH/NIA R01AG086363 $76,637,320
Alzheimer's Prevention Initiative ADAD Colombia Trial

**Valentina Ghisays (Co-I)** 04/2024-03/2029
NIH/NIA R01AG086363 $76,637,320
Alzheimer's Prevention Initiative ADAD Colombia Trial

**Valentina Ghisays (Co-I)** 07/01/2024-06/30/2025
Arizona DHS via Arizona Alzheimer's Consortium $100,000
Statistical and Neuroimaging Data Science Core Resources Serving the Consortium Members

**Valentina Ghisays (Project PI)** 07/01/2024-06/30/2025
Arizona DHS via Arizona Alzheimer's Consortium $44,444
Impact of Apolipoprotein E on Alzheimer's Disease and Related Dementia Risk in Understudied Populations from Real-World and Biomarker-Characterized Study Cohorts

**Yi Su (Co-I)** 04/2024-06/2029
NIH/NINDS via Boston University $15,538,237
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

**Yi Su (Co-I)** 04/01/2024-03/31/2029
NIH/NIA $76,637,320
R01AG086363 (Alexander/Reiman/Langbaum/Lopera)
Alzheimer's Prevention Initiative ADAD Colombia Trial Program

**Yi Su (Co-I)** 04/2025-03/2030
NIH/NIA via ASU R01AG092647 (Wu) $3,802,086
Multi-Scale Modeling of Aging and Alzheimer's Disease

**Yi Su (Co-I)** 07/01/2024-06/30/2025
Arizona DHS via Arizona Alzheimer's Consortium $100,000
Statistical and Neuroimaging Data Science Core Resources Serving the Consortium Members

**Yi Su (Co-I)** 07/01/2024-06/30/2025
Arizona DHS via Arizona Alzheimer's Consortium $177,778
Advanced Imaging Data Analysis and ML/AI in Alzheimer's Research

**Alireza Atri (Project Co-I)** 07/01/2024-06/30/2025
Arizona Alzheimer's Consortium via Arizona DHS (Choudhury) $44,444 Total Project
Trajectories of clinical symptoms and associations with pathology in Lewy body spectrum disorders

**Alireza Atri (Project PI)** 07/01/2024-06/30/2025
Arizona DHS via Arizona Alzheimer's Consortium (Atri) $186,667 Total Project
Clinical Phenotyping and Biological Characterization of The Longevity Cohort Study: Global Staging and Biospecimen Banking

**Alireza Atri (Project PI)** 07/01/2024-06/30/2025
Arizona Alzheimer's Consortium via Arizona DHS (Atri) $27,778 Total Project
Development, Validation and Implementation of Cognitive and Clinical Composites for the Arizona Study of Aging and Neurodegenerative Disorders/BBDP

**Alireza Atri (Project PI)** 07/01/2024-06/30/2025
Arizona DHS via Arizona Alzheimer's Consortium (Atri) $82,222 Total Project
Shared Resource of Research Participants Data and Biological Samples for Study of Alzheimer's Disease

**Geidy Serrano (Co-I)** 09/01/2024-08/30/2026
ASAP/MJFF ASAP-000301 (Scherzer) $155,143 Total Project
Parkinson5D: deconstructing proximal disease mechanisms across cells, space, and progression (Extension)

**Geidy Serrano (Co-I)** 12/01/2024-11/30/2029
NIH R01 via UAB (Hinman) $1109,931 Total Project
Defining the molecular spectrum of white matter vascular lesions

**Geidy Serrano (Co-I)** 07/01/2024-06/30/2029
NIH via Stanford University 1R01AG088656-01 (Jaiswal) $220,362 Total Project
Uncovering mechanisms of protection from Alzheimer's disease in CHIP using human cohorts and biosamples

**Geidy Serrano (Co-I)** 12/01/2024-11/30/2029
NIH via University of Arizona (Miller) $459,797 Total Project
Neurogenetics of Aging Vocalizations and Relevance to Neurodegenerative Diseases

**Geidy Serrano (Co-PI)** 09/01/2024-08/31/2026
MJFF-025460 (Beach) $647,836 Total Project
Synuclein CSF SAA and Biofluids AD Biomarkers within the Arizona Study of Aging and Neurodegenerative Disorders

**Geidy Serrano (Co-PI)** 09/01/2024-08/31/2029
NIH via TGEN (Huentleman/Serrano) $709,820 Total Project
Drug repositioning for Alzheimers disease using genomic data from multiple brain regions

**Geidy Serrano (Site PI)** 12/01/2024-11/30/2029
NIH via UC Irvine RF1AG029479 (Mukherjee) $250,000 Total Project
PET Imaging agents for a4b2 Nicotinic Receptors

**Parichita Choudhury (Co-PI)** 07/01/2024-06/30/2025
Lewy Body Dementia Association (Choudhury/Chiu) $12,500 Total Project
Research Center of Excellence Program Award
TBD renewable annually

**Thomas Beach (Co-I)** 09/01/2024-08/30/2026
ASAP/MJFF ASAP-000301 (Scherzer) $155,143 Total Project
Parkinson5D: deconstructing proximal disease mechanisms across cells, space, and progression (Extension)

**Thomas Beach (Co-I)** 04/01/2025-03/31/2027
NIH via UCLA 1R21NS137072 - 01 (Bitan) $49,532 Total Project
A novel diagnostic assay for rare parkinsonian tauopathies

**Thomas Beach (Co-I)** 04/01/2025-03/31/2030
NIH via University of Hawaii 1R01CA276728-01 (Wu) $117,002 Total Project
Uncovering causal protein markers to characterize pancreatic cancer etiology and improve risk prediction

**Thomas Beach (Co-I)** 07/01/2024-06/30/2028
NIH via ASU 1U01AG089184-01 (Sierks) $252,462 Total Project
A Novel Multiparameter Blood Test for Early Detection of Alzheimer's disease and Frontotemporal Dementia

**Thomas Beach (Co-I)** 07/01/2024-06/30/2026
NIH SBIR via Virtici LLC (Fanger) $74,160 Total Project
A Novel Blood Test for Early Diagnosis of Frontotemporal Lobar Degeneration

**Thomas Beach (Co-I)** 07/01/2024-06/30/2029
NIH via Stanford University 1R01AG088656-01 (Jaiswal) $220,362 Total Project
Uncovering mechanisms of protection from Alzheimer's disease in CHIP using human cohorts and biosamples

**Thomas Beach (Co-I)** 09/01/2024-08/31/2029
NIH via TGEN (Huentelman/Serrano) $709,820 Total Project
Drug repositioning for Alzheimers disease using genomic data from multiple brain regions

**Thomas Beach (Co-I)** 04/01/2025-03/31/2026
NIH via Rush University Medical Center R01NS142276 (Killinger) $35,617 Total Project
Defining the Role of Alpha-Synuclein Phosphorylation in the Synucleinopathy Olfactory System

**Thomas Beach (Co-I)** 04/01/2025-03/31/2030
NIH via St. Jude Children's Research Hospital (Peng) $194,875 Total Project
Proteogenomics of Splicing Proteinopathies in Neurodegeneration

**Thomas Beach (Co-I)** 12/01/2024-11/30/2029
NIH via VAI 1R01NS142166-01 (Henderson) $82,791 Total Project
Molecular dissection of Parkinson's disease progression

**Thomas Beach (Co-I)** 12/01/2024-11/30/2029
NIH via UT Health 1R01AG091615-01 (Soto) $173,534 Total Project
Alpha-synuclein seed amplification assay as a biomarker for Lewy body dementia and Alzheimer's disease

**Thomas Beach (Co-I)** 12/01/2024-11/30/2029
NIH via University of Arizona (Miller) $459,797 Total Project
Neurogenetics of Aging Vocalizations and Relevance to Neurodegenerative Diseases

**Thomas Beach (Co-I)** 04/01/2025-03/31/2030
NIH via Rush University Medical Center (Romanova) $165,592 Total Project
Arachnoid barrier in Alzheimer's disease

**Thomas Beach (Co-I)** 12/01/2024-11/30/2029
NIH via University of Alabama Birmmingham (Goldberg) $108,360
Role of vascular mitophagy in Alzheimer's disease and its related dementias

**Thomas Beach (PI)** 09/01/2024-08/31/2026
MJFF-025460 (Beach) $647,836 Total Project
Synuclein CSF SAA and Biofluids AD Biomarkers within the Arizona Study of Aging and Neurodegenerative Disorders

**Robert Alexander (PI), Eric Reiman (PI), Jessica Langbaum (PI), Pierre Tariot (Co-I), Yi Su (Co-I), Valentina Ghisays (Co-I)** 09/01/2024-08/31/2029
1R01AG086363-01 $74,457,897
NIH
Alzheimer's Prevention Initiative ADAD Colombia Trial Program

**Eric Reiman (PI)** 09/01/2024-08/31/2025
1OT2OD037642-01 $4,900,000
University of Arizona-Banner Health Mountain Consortium