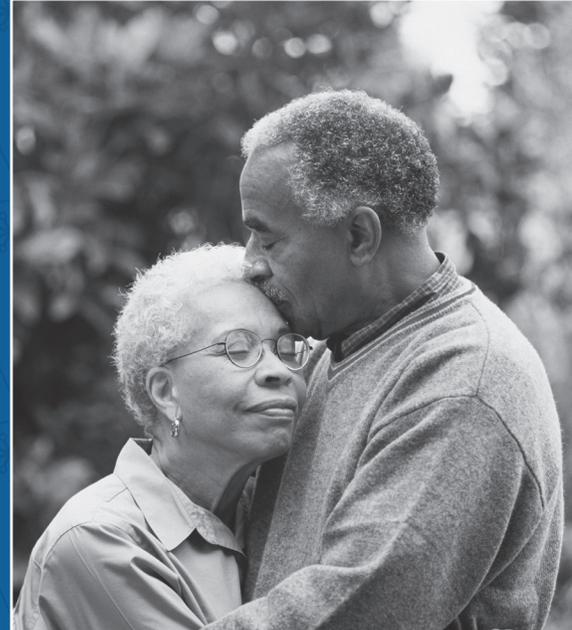


2022

Arizona Alzheimer's Consortium

Scientific Conference
Abstracts & Annual Report

Hosted by Arizona State University
Sept. 22, 2022



ARIZONA
ALZHEIMER'S
CONSORTIUM



**ARIZONA
ALZHEIMER'S
CONSORTIUM**

Annual Report

July 1, 2021 - June 30, 2022

and

23rd Annual Scientific Conference

September 22, 2022

Table of Contents

Introduction to Annual Report.....	Page 4
Annual Scientific Conference	
Agenda.....	Page 13
Oral Presentation Abstracts.....	Page 32
Poster Presentation Abstracts.....	Page 45
Additional Accepted Abstracts.....	Page 183
Institutional Research Summaries & Personnel.....	Page 196
Project Progress Reports by Institution.....	Page 239
Publications and Manuscripts.....	Page 459
Current and Pending Grants.....	Page 507
Institutional Budgets and Justifications.....	See Companion Report

In Memory of our Dear Colleague



Geoffrey L. Ahern, M.D., Ph.D.

1954-2022



Introduction to the Annual Report

Background

The Arizona Alzheimer's Consortium is the nation's leading model of statewide collaboration in Alzheimer's disease (AD) research. It includes more than 150 researchers and staff from seven principal organizations: Arizona State University, Banner Alzheimer's Institute, Banner Sun Health Research Institute, Barrow Neurological Institute, Mayo Clinic Arizona, the Translational Genomics Research Institute, and the University of Arizona, four formally affiliated organizations: Critical Path Institute, Midwestern University, Northern Arizona University/TGen North, and the University of Arizona College of Medicine, Phoenix, and prospective affiliated organizations, like Banner Alzheimer's Institute-Tucson, and the Phoenix and Southern Arizona Veterans Administration Health Systems. Established in 1998, the Consortium is intended to make a transformational difference in the scientific fight against AD and AD-related disorders (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 blood-based biomarkers (BBBMs) in these and related endeavors. Its primary goal is to find effective AD prevention therapies as soon as possible.

The Consortium is widely recognized as a model of multi-institutional collaboration in biomedical research. Its researchers capitalize on expertise and resources from complementary disciplines and organizations to address scientific problems in the most impactful ways. It receives critical support from the state of Arizona (through the Arizona Department of Health Services [ADHS]), the participating organizations, the National Institute on Aging (NIA)-sponsored Arizona AD Research Center (ADRC), and numerous other grants, contracts, and organizational and philanthropic investments.

Eric Reiman is Director of the Consortium and the NIA-sponsored ADRC; Richard Caselli and Jessica Langbaum are the ADRC's Associate Directors; Carol Barnes chairs the Consortium's 24-member Internal Scientific Advisory Committee (ISAC); and Jeffrey Kordower will chair ISAC during Dr. Barnes's 2022-2023 sabbatical. David Jerman is Administrative Director of the Consortium's state and organizationally supported research Consortium, Andrea Schmitt is Administrative Director of the NIA-sponsored Arizona ADRC. Administrative leaders from each of the seven principal organizations serve on the Consortium's Board of Directors. The Consortium's external advisors include Drs. Marilyn Albert, Zaven Khachaturian, Bruce Miller, and Thomas Montine, who are internationally recognized for their contributions to and leadership roles in the study of AD and/or related disorders. They conduct annual site visits, review the progress and productivity of both the Consortium and ADRC, and provide formal feedback and recommendations to researchers, NIA, and the state of Arizona.

The Arizona Alzheimer's Consortium capitalizes on the state's strengths in brain imaging, emerging blood-based and other biomarkers, genomics, the computational, mathematical, statistical, artificial intelligence/machine learning, and big data analyses of complex data sets, the basic, 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 stakeholders from different organizations 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 AD research and care.

State and organizational matching funds continue to provide the “glue” for this geographically distributed research program, 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 include researchers from 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 played a prominent role with continuous funding in the highly competitive National AD Research Centers Program. Our current Arizona ADRC grant (from September 1, 2021 to June 30, 2026) provides increased funding, growing emphases on AD biomarkers, the study of research participants from under-represented, and mechanisms to support the development of promising researchers from diverse backgrounds in the scientific fight against AD. Our new ADRC includes Administrative, multi-site Clinical, Data Management and Statistics (DMS), Biomarker, Neuropathology, and Outreach, Recruitment and Engagement (ORE) Cores, Developmental Projects, and a Research Education Component (REC). For the first twenty years, our NIA-sponsored Center focused on the early detection and prevention of AD. Our current ADRC places additional emphases on the development of emerging BBBMs for the diagnosis, preclinical study, and prevention of AD/ADRD, and their generalizability to underrepresented 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; and 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 NIA ADRC grant, NIA grant for the study of cognitively unimpaired persons at six levels of genetic risk based on their APOE genotype, Gates Ventures grant, and state, organizational and philanthropic funds will 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. These funds support our efforts to 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. Furthermore, these funds enable us to provide resources to support studies of preclinical AD and nonpathological aging in our cognitively unimpaired participants at differential genetic and/or biomarker risk 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, our researchers have generated thousands of publications, grants, and contracts, as well as more than \$2 billion in new investments. We have made pioneering contributions to the study of AD and ADRD, along with that of the aging mind and brain:

1. We have helped clarify genetic and non-genetic (e.g., microbial) risk, resilience, and resistance factors and disease mechanisms, offered targets at which to aim new AD treatments, provided new insights about the pathological changes associated with AD and ADRD, and provided targets for the discovery of drug and gene therapies to treat and prevent AD.
2. We 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. We 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/>), and online memory tests and other information that has been generated in >225,000 participants in the MindCrowd project (www.mindcrowd.org).
4. We have and continue to hold 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. We have introduced new research paradigms, image-analysis techniques,

and other approaches to help in this endeavor. Our researchers have both anticipated and advanced the conceptualization of preclinical AD.

i. We 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 have begun to extend this effort to persons at six levels of genetic risk (including those with one or two copies the relatively protective APOE2 allele) and support the study of persons who remain cognitively unimpaired at older ages despite their genetic risk.

ii. We have worked with our Colombian colleagues to establish the Colombian Alzheimer's Prevention Initiative (API) registry of about 6,000 persons from the world's largest Autosomal Dominant AD (ADAD) kindred, 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 ADAD prevention trial. We have begun to provide invaluable resources of data, biological samples to advance the preclinical study and prevention of AD and helped launch a new era in AD prevention research.

5. We 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. We 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.

6. We 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. We have also begun to develop resources and tools to support the development of and evaluate promising CSF assays, blood tests, and mobile technologies as soon as possible.

7. We continue to hold 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 blood-based biomarker 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.

8. We 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 related disorders in the Brain and Body Donation Program. As previously noted, we have begun to incorporate ante-mortem biomarkers and new brain tissue resources to help researchers address their goals with even greater impact.

9. We 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. We 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 use this shared resource to support the generalizability of these tests to under-represented Hispanic/Latino and American Indian groups. We 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.

10. We have begun to characterize cognitive, biomarker, neuropathological, and other effects of COVID-19 infection in living persons and expired brain donors, and we 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]").

11. We continued leadership efforts for the Alzheimer's Prevention Initiative (API) to set the stage for a new era in AD prevention research, including NIH- and industry supported prevention trials of putative AD-modifying treatments in cognitively unimpaired persons at genetic risk, later expanding to trials in people at biomarker risk for AD. API 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 wide-reaching research registries and APOE gene-matching programs to support interest and enrollment in AD-focused studies, and new prevention trials that provide a realistic chance to find and support the accelerated approval and availability of prevention therapies within the next five years.

i) With support from NIA, Genentech/Roche, and philanthropy, the API Autosomal Dominant AD (ADAD) Colombia Trial of the anti-oligomeric amyloid antibody therapy crenezumab was recently completed in 252 cognitively unimpaired PSEN1 E280A amyloid-positive and negative mutation carriers who were randomized to active treatment or placebo and non-carriers who were assigned to placebo. The world's first AD prevention trial in persons at genetic risk, it introduced scientific, social, ethical, and risk disclosure strategies to accelerate the evaluation and approval of effective AD prevention therapies; it established a registry with about 6,000 members of the PSEN1 E280A kindred, and the clinical trials, PET and MRI infrastructure needed to conduct the trial; and it demonstrated the ability to evaluate an experimental treatment in vulnerable persons from a developing country in ways that the participants and families valued. Indeed, 94% of trial participants completed the 5–8-year study. While annualized mean changes in clinical, cognitive and biomarker endpoints consistently favored crenezumab treatment over placebo and BBBM assays have not yet been completed, there were no statistically significant differences in any of the available measurements. Despite the disappointing results, this trial showed that AD prevention trials were possible, introduced ways to accelerate the evaluation and approval of investigational prevention therapies, led to a growing number of prevention trials led by API and other groups, and have thus given the field a fighting chance to find effective prevention therapies within the next few years. Shared data and biological samples from the trial will inform the design of new prevention trials inside and outside of Colombia, including those that API would like to initiate within the next 18 months, further inform ongoing prevention trials, and further inform the study of preclinical AD.

ii) With support from NIA, Novartis/Amgen, and philanthropy, API Generation Study 1 was evaluating the BACE1 inhibitor umibecestat (an oral anti-amyloid production drug) and active immunization (vaccine) therapy CAD106 in cognitively unimpaired amyloid-positive and amyloid-negative APOE4 homozygotes; API Generation Study 2 had been evaluating umibecestat in additional cognitively unimpaired APOE4 amyloid-positive and amyloid-negative homozygotes and amyloid-positive APOE4 heterozygotes. The trials were discontinued early due to mild cognitive worsening in association with high-dose BACE inhibition (which turned out to be a class effect). Follow-up assessments found that the cognitive worsening was reversible and raised the possibility of using lower BACE inhibitor doses in future prevention trials. The vaccine therapy was recently found to reduce amyloid plaque deposition, supporting the potential value of amyloid vaccine therapies in the prevention of AD. De-identified trial data and biological samples will be shared with the field.

iii) Researchers from Roche, API, Massachusetts General Hospital, and the University of Southern California have initiated the Skyline Trial, an AD prevention trial of the amyloid plaque-reducing treatment gantenerumab in cognitively unimpaired persons with PET or CSF evidence of amyloid plaques, and 2 NIA-funded ancillary studies. The study includes an optional BBBM prescreening mechanism to reduce the amyloid screen fail rate in the trial. In addition to contributing to trial design, NIA funds are intended to provide a shared resource of data and blood samples to support BBBM development and provide more scalable ways to inform cognitively unimpaired persons about their genetic and biomarker results and associated risk of developing

dementia due to AD. If pivotal trials of gantenerumab in mildly impaired patients demonstrate a clinical benefit when initial findings are reported this fall, the prevention trial will have an excellent chance to find and support the accelerated approval of an AD prevention therapy within the next few years.

iv) With support from Lilly, Lilly and API have initiated Trailblazer ALZ-3, a potentially groundbreaking “decentralized” AD prevention trial of the company’s amyloid plaque-reducing antibody treatment donanemab in cognitively unimpaired adults. The trial uses Lilly’s plasma p-tau217 assay to identify individuals who are amyloid-positive. The decentralized design allows participants and their study partners to complete their cognitive and clinical assessments virtually without having to travel to a study site, thereby supporting the inclusion of persons from more remote locations and underrepresented groups. In a Phase 2 Trial, donanemab was suggested to reverse PET evidence of amyloid-plaque deposition, reduce plasma p-tau concentrations (an indicator of amyloid-related tau pathophysiology), and slow clinical decline. If the pivotal trial of donanemab in mildly impaired patients demonstrate a clinical benefit when initial findings are reported in early 2023, the prevention trial will have an excellent chance to find and support the accelerated approval of an AD prevention therapy within the next few years.

v) API includes exceptionally large registries and related programs to support enrollment in AD prevention trials and related research studies. It includes the Colombian API Registry with about 6,000 PSEN1 E280A mutation carriers and non-carriers from the world’s largest ADAD kindred, including nearly 1,200 mutation carriers who are virtually certain to develop AD and become cognitively impaired at the median age of 44. It includes the web-based Alzheimer’s Prevention Registry with more than 380,000 members (www.endALZnow.org) and its GeneMatch with more than 100,000 members who have undergone APOE genotyping. API also leads the development and evaluation of novel risk disclosure programs to support enrollment into AD prevention trials. These and related efforts continue to have a profound impact on researchers, policy makers, and other stakeholders around the world.

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

Emerging Developments, Opportunities and Initiatives

Amyloid Plaque-Reducing Treatments. In the last few years, pivotal clinical trials have evaluated four promising but not yet definitely proven amyloid plaque-reducing antibody therapies in patients with mild cognitive impairment (MCI) and mild dementia due to AD. One of the drugs (aducanumab) was prematurely discontinued based on an initial futility analysis, subsequently suggested but not proven to have a clinical benefit based on findings from one trial and post-hoc findings from another trial, granted accelerated approval by FDA based on its judgment that this and other amyloid plaque-reducing benefits are “reasonably likely” but not certain to have a clinical benefit, but will not be covered by the Centers for Medicare and Medicaid Services (CMS) and many other payers without additional studies. Readouts from potentially license-enabling trials of lecanemab, gantenerumab, and donanemab are expected this fall and early next year.

If the above mentioned treatments demonstrate a clinical benefit, it will be a game changer for the field, as it will confirm the role of certain amyloid aggregates in the pathogenesis, treatment,

and potential prevention of AD. Trial data, samples, and findings from this work will clarify those biological effects that are associated with a clinical benefit, enable therapeutic biomarkers to inform the development of promising AD-modifying treatments in clinical trials, and accelerate the evaluation and approval of these and eventually other treatments in the prevention of AD using surrogate biomarker endpoints that are reasonably likely to predict a clinical benefit. It could also lead more primary care providers to ask their patients about memory and thinking problems during their annual wellness visits and take proactive steps to better address their medical and non-medical needs. If these treatments do not show a clinical benefit, ongoing prevention trials of these and other anti-amyloid treatments will be needed to determine if these treatments might be helpful before the disease is extensive.

If the drugs are effective, additional efforts will be needed to support their affordability and widespread accessibility, including in under-served communities and developing countries; find ways in which more affordable and accessible blood tests or other biomarker strategies could reduce the need for expensive amyloid PET scans and more invasive lumbar punctures; and manage the drug's most common side effect (amyloid-related imaging abnormalities [ARIA]). The field would capitalize on these findings to clarify which biomarker endpoints are associated with a clinical benefit, use them to inform AD treatment development, and further accelerate the evaluation and approval of AD prevention therapies. If the drugs are not effective, there will still be a need to complete the prevention trials of these and certain other anti-amyloid treatments, consider the potential benefits of combination or sequential treatment with anti-amyloid and other treatments that target downstream (e.g., tau, inflammatory or neurodegenerative) processes; and continue to diversify the portfolio of AD-modifying treatments. For these and other reasons, the field is eager to see the upcoming pivotal trial findings and understand their potential impact on the field.

During the past year, ASU and BAI collaborated with Ara Khachaturian and Zaven Khachaturian and a wide range of thought leaders to consider what it would take support the affordability and widespread accessibility to AD prevention therapies, should we or others find effective AD prevention therapies within the next few years. They held a virtual symposium and published initial recommendations. They have also been working with a leading health economist from the University of Southern California to assess the financial impact of different kinds of prevention therapies and further support their affordability. We believe that recommendations and cost estimates are needed even before prevention therapies are considered for regulatory agency approval and payer coverage.

Blood tests. We continue to advance the development of BBBMs of amyloid plaque deposition (e.g., plasma amyloid- β 42/40 [A β 42/40]), A β -mediated tau pathophysiology and the diagnosis of AD (e.g., plasma ptau217, 231 or 181), the neuronal injury and neurodegenerative changes observed in persons with AD and a wide range of neurological disorders (e.g., plasma or serum NfL), and other pathophysiological features of AD (e.g., plasma GFAP, an indicator of astrogliosis). More work is needed to refine, evaluate, and compare these BBBMs to clarify their role in AD research, treatment development, and clinical care. Still more work is needed to find BBBMs for ADRD (including indicators of alpha-synuclein/Lewy body pathophysiology, TDP-43 pathology, and cerebrovascular disease). Like effective AD-modifying drugs, blood tests could have transformational effects in AD research, treatment, development, and care. As previously noted, we continue to play major roles in the effort to fulfill the promise of BBBMs in AD research, treatment development, and clinical care, and extend their value to research participants, patients, and families from under-represented groups. We 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." We are extremely excited about this new grant, which is intended to bring together researchers from across the country to better understand 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 we follow several important research cohorts in our longitudinal studies and prevention trials, the value of our cohorts would be dramatically increased by the incorporation of biomarkers, CSF, and blood samples to characterize amyloid, tau, neurodegenerative and cerebrovascular disease burden, and, when available, ADRC (e.g., alpha-synuclein and TDP-43) pathologies. As illustrated above, we have invested in several initiatives to address this challenge and have the greatest possible impact.

Increasing the study of our underrepresented 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 formed a partnership 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 underrepresented groups. Based on our recent progress in the recruitment of interested American Indian and Hispanic/Latino research participants, we plan to apply for an Administrative Supplement to our ADRC grant to provide a shared resource of data and samples in 100 American Indian and 100 Hispanic/Latino research participants. We will seek to clarify the accuracy of promising BBBMs of amyloid plaque deposition and amyloid-mediated tau tangle burden using amyloid and tau PET scans as "standards of truth;" establish a local advisory group and support the acquisition and sharing of data and biological samples in ways that advance the fight against AD in ways that protect indigenous data sovereignty.

Promoting the development of new investigators. Consistent with the new round of Requests for AD Research Center (ADRC) grant applications, we have placed a growing emphasis on recruitment and mentorship of new investigators, including young student and faculty investigators, established investigators who are new to our field, and a growing number of investigators from under-represented groups. Our programs include our NIH-supported, AD/ADRD-related post-doctoral and pre-doctoral research training programs, support for competitive pilot study grant applications, courses in the conduct of relevant research studies, and other outreach, educational and research internship programs for students from a wide range of ages and backgrounds. We also begun to conduct a highly innovative collaborative training and research program for promising new investigators, including those from diverse backgrounds within the new ADRC's REC, provide support for their participation in relevant conferences and retreats; and support their research career development in other ways.

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 their 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.

Looking Ahead

We and our colleagues will continue to develop new scientific and clinical initiatives and advance our existing programs; we continue to attract, diversify, and support the development of great researchers and clinicians; and we have been honored to secure the state, organizational, philanthropic and federal investments needed to fulfill our ambitious goals. 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. Along with the study and treatment of cognitive 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 foster push-pull relationships between research applications and methodological development and between brain omics and other observational studies in human subjects and basic science studies in experimental models. We will continue to develop and extensively shared resources from our different programs, and do so in appropriate and culturally sensitive ways, to have the greatest possible impact.

We will continue to support the development, testing and comparison of BBBMs for AD and ADRD and use them in innovative ways, such that they can 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, BBB 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. We think the field has a chance to develop new gene therapies and the mechanism needed to deliver them to the right brain cells within the next five years and put promising gene-silencing antisense oligonucleotide and RNAi treatments to the test in informative early phase treatments along the way. We look forward to the continued diversification in AD-modifying treatments, including those that target APOE, and the chance to put them to test with greater speed and statistical power in early phase trials.

We will continue to support the diversification of research participants researchers, and clinicians in the fight against AD and capitalize on this diversity in highly impactful ways. We will continue to generate invaluable resources of data, including antemortem and postmortem biological samples as well as interested research participants, and forge new collaborations in support of these and other goals.

As we noted last year, we and our colleagues have a chance to demonstrate the efficacy of amyloid plaque-reducing antibody therapies, provide compelling support for a role of amyloid in the development, treatment, and prevention of AD, and find those theragnostic biomarker endpoints that are associated with a clinical benefit. We have a chance to use those biomarkers to further inform, accelerate, and support the successful development of new treatments in non-clinical and early phase trials, accelerate the evaluation of AD-modifying and prevention therapies, and clarify the mechanisms by which lifestyle interventions and repurposed drugs exert their cognitive-health promoting effects. While there are no guarantees, we still have a chance to find and support the accelerated approval of an effective AD therapy within the next few years, even by 2025. We are excited about the chance to play important roles in these and other in these and other endeavors.

We are extremely grateful to the state of Arizona, our participating organizations, NIH and all our other supporters for giving us the chance to make a profound difference in the scientific and clinical fight against AD/ADRD and find effective prevention therapies as soon as possible.

Arizona Alzheimer's Consortium
23rd Annual Scientific Conference – Thursday September 22nd, 2022
Arizona State University (Host Institution)
Memorial Union
301 E Orange St., Tempe, AZ 85281

8:15 – 9:30 AM POSTER PRESENTATION SET-UP & CONTINENTAL BREAKFAST

9:30 – 9:40AM WELCOME

Matthew Hulver PhD, Vice President & Professor, ASU Knowledge Enterprise and Vice President & Professor, College of Health Solutions
Dr. Hulver is responsible for identifying and deploying strategies to grow and diversify ASU's research enterprise.

9:40 – 10:00AM INTRODUCTION

Eric M. Reiman, M.D.
CEO, Banner Research
Director, Arizona Alzheimer's Consortium

10:00 – 11:15AM LEON THAL MEMORIAL LECTURE

**New Discoveries in the Preclinical Phase of Alzheimer's Disease:
Findings from the Wisconsin Registry for Alzheimer's Prevention**

Sterling Johnson, PhD
Jean R. Finley Professor of Geriatrics and Dementia
Principal Investigator for the WRAP Study
Associate Director, Wisconsin Alzheimer Disease Research Center
University of Wisconsin School of Medicine and Public Health

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

12:30 PM Students 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, M.D.

**Arizona Alzheimer's Consortium
23rd Annual Scientific Conference**

Oral Research Presentations

SESSION I Moderators: Heather Bimonte-Nelson, PhD & Zaven Khachaturian, PhD

- 11:15 – 11:26 AM **Initial findings from the Alzheimer's Prevention Initiative Autosomal Dominant Alzheimer's Disease Colombia Trial.** Presenting Author: Jessica Langbaum, PhD, Banner Alzheimer's Institute
- 11:27 – 11:38 AM **Effects of aerobic exercise on cognition and imaging biomarkers in older adults with Alzheimer's disease dementia.** Presenting Author: Fang Yu, PhD, RN, GNP-BC, FGSA, FAAN, Arizona State University
- 11:39 – 11:50 AM **Clinical predictors of Alzheimer's disease development in patients with mild cognitive impairment, using synthetic data derived from Veterans Affairs electronic health records.** Presenting Author: Chase Irwin, MS, University of Arizona – College of Medicine-Phoenix
- 11:51 – 12:02 PM **Statin responder analysis for precision prevention of Alzheimer's disease.** Presenting Author: Georgina Torrandell-Haro, University of Arizona
- 12:03 – 12:14 PM **Heparin treatment is associated with a delayed diagnosis of Alzheimer's dementia in electronic health records from two large United States health systems.** Presenting Author: Benjamin Readhead, MBBS, Arizona State University
- 12:15 – 12:26 PM **Cerebral microvascular dysfunction in 5x-FAD mice: role of biological sex, BK channel activity and oxidative stress.** Presenting Author: Josiane Fernandes da Silva, PhD, University of Arizona

**Arizona Alzheimer's Consortium
23rd Annual Scientific Conference**

Oral Research Presentations

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

- 3:00 – 3:11 PM **Deep learning application in retinal imaging classification of Alzheimer's disease.** Presenting Author: Oana M. Dumitrascu, MD, MSc, Mayo Clinic Arizona
- 3:12 – 3:23 PM **Longitudinal motor decline in Dementia with Lewy Bodies and Parkinson's Disease Dementia in the Arizona Study of Aging and Neurodegenerative Disease.** Presenting Author: Parichita Choudhury, MD, MSc, Banner Sun Health Research Institute
- 3:24 – 3:35 PM **Advancing Evidence-based ADRD Caregiver Interventions through Technology.** Presenting Author: Abigail Gómez-Morales, Arizona State University
- 3:36 – 3:47 PM **Neurogenetics of aging voice and implications for neurodegenerative diseases.** Presenting Author: Julie E. Miller, PhD, University of Arizona
- 3:48 – 3:59 PM **Florbetapir PET Measurements of amyloid plaques deposition are more closely correlated with cross-sectional and longitudinal cognitive and clinical measurements using a white matter reference region-of-interest.** Presenting Authors: Vedanshi Bhargava and Michele Wang, University of Arizona College of Medicine-Phoenix
- 4:00 – 4:11 PM **Head-to-head comparison of four plasma phospho-tau immunoassays in the neuropathological diagnosis of Alzheimer's disease.** Presenting Author: Michael Malek-Ahmadi, PhD, MSPH, Banner Alzheimer's Institute

Student Poster Presentations

1. **ADULTHOOD CHOLINE SUPPLEMENTATION IN THE TS65DN MOUSE MODEL OF DOWN SYNDROME.** Tallino SL, Bartholomew SK, Sepulveda I, Winstone JK, Velazquez R. Arizona State University; Arizona Alzheimer's Consortium.
2. **AGE-RELATED ALTERATIONS IN REPRESENTATIONAL FORMS OF IMAGINATION: A NOVEL SCORING PROTOCOL APPLIED TO AUTOBIOGRAPHICAL MEMORY.** Hovhannisyan M, Chau N, Deffner A, Andrews-Hanna JR, Grilli MD. University of Arizona; Arizona Alzheimer's Consortium.
3. **AGING-ASSOCIATED MEDIN INDUCES HUMAN BRAIN MICROVASCULAR ENDOTHELIAL CELL PRO-INFLAMMATORY AND PRO-THROMBOTIC ACTIVATION VIA NFKB.** Nabaty NL, Karamanova N, Truran S, Morrow K, Schafer R, Li M, Migrino RQ. University of Arizona College of Medicine-Phoenix; Phoenix VA; Arizona Alzheimer's Consortium.
4. **AGING WITH TRAUMATIC BRAIN INJURY: EVALUATION OF NEUROPATHOLOGY, AXONAL INJURY, NEUROINFLAMMATION, AUTOPHAGY, AND PTAU PATHOLOGY IN THE DENTATE GYRUS AT 6-MONTHS POST-INJURY.** Rajaboina B, Krishna G, Mian E, Sabetta Z, Bromberg C, Baun J, Zurhellen C, Adelson PD, Currier Thomas T. University of Arizona College of Medicine-Phoenix; Barrow Neurological Institute at Phoenix Children's Hospital; Arizona State University; Neuroscience Associates; Phoenix VA Health Care System; Arizona Alzheimer's Consortium.
5. **ANALYSIS OF MICROSTRUCTURAL FEATURES OF BONNET MACAQUE LOCUS COERULEUS- CENTRAL TEGMENTAL TRACT USING MRI MICROSCOPY.** McDermott K, Laurel Dieckhaus L, Gray DT, Hutchinson EB, Barnes CA. University of Arizona; University of California, Los Angeles; Arizona Alzheimer's Consortium.
6. **APOE ϵ 4-ALLELE IS ASSOCIATED WITH REDUCED HIPPOCAMPAL VOLUME IN OLDER ADULTS WITH AUTISM SPECTRUM DISORDER.** Al-Hassan L, Lewis, C, Braden BB. Arizona State University; Arizona Alzheimer's Consortium.
7. **BINDING AND DISRUPTION OF AMYLOID BETA AND TAU PLAQUES VIA FOCUSED ULTRASOUND AND TARGETED PHASE SHIFT MICROBUBBLES IN A MOUSE MODEL OF ALZHEIMER'S DISEASE.** Murphy D, Howison C, Lusk J, Unger E, Meuillet E, Trouard T. University of Arizona; Microvascular Therapeutics; Arizona Alzheimer's Consortium.
8. **CELLULAR MODELS FOR THE INVESTIGATION OF STRUCTURAL DYNAMICS AND ACTIVITY OF HUMAN TAU PROTEIN AGGREGATE FORMATION.** Ranaweera E, Huseby CJ, Hansen DT, Chiu PL, Serrano GE, Beach TG, Fromme P. Arizona State University; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

9. **COGNITIVE EFFECTS OF UNOPPOSED ESTROGENIC HORMONE THERAPY IN TWO RODENT MODELS OF SURGICAL MENOPAUSE.** Asadifar S, Bernaud VE, Wu ES, Bandin EA, Peña VL, Pastor JA, Highton LE, Andrew KB, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.
10. **DATA MINING THE NATIONAL ALZHEIMER'S COORDINATING CENTER (NACC) UNIFORM DATA SET TO DETERMINE ASSOCIATIONS BETWEEN MRI AND DEMENTIA.** Schatz S, Comrie C, Dieckhaus L, Hutchinson E. University of Arizona; Arizona Alzheimer's Consortium.
11. **DECONSTRUCTING THE BLOOD BRAIN BARRIER: EVALUATION OF CORTICAL ASTROCYTIC CHANGES SURROUNDING MICROVASCULATURE POST-TBI.** Sabetta Z, Krishna G, Willayard FA, Curry T, Adelson PD, Thomas TC. University of Arizona; Barrow Neurological Institute at Phoenix Children's Hospital; Phoenix VA Healthcare System; Arizona State University; Midwestern University; Arizona Alzheimer's Consortium.
12. **DESIGNING A METHOD OF PRIME INDUCED NUCLEOTIDE ENGINEERING USING A TRANSIENT REPORTER FOR EDITING ENRICHMENT (PINE-TREE).** Kostes W, Frisch C, Galyon B, Whitman B, Brafman D. Arizona State University; Arizona Alzheimer's Consortium.
13. **DEVELOPMENT OF NONLIPOGENIC ABCA1 INDUCERS AS ALZHEIMER'S DISEASE THERAPEUTICS.** Laham M, Lewandowski C, LaDu MJ, Reddy VG, Ackerman-Berrier M, Rychetsky P, Penton C, Reddy MS, Thatcher G. University of Arizona; University of Illinois at Chicago; Arizona Alzheimer's Consortium.
14. **DUAL AMELIORATION OF NEUROFIBRILLARY TANGLES AND AMYLOID PLAQUES WITH DYR219: A POTENT AND SELECTIVE SMALL MOLECULE FOR DYRK1A.** Alessandra Fistrovich, Christopher Foley, Ronald Velasquez, Ow A, Oddo S, Meechoovet B, Dunckley T, Shaw A, Smith B, Hulme C. University of Arizona; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.
15. **EFFECT OF ADUCANUMAB-MEDIATED AMYLOID CLEARANCE ON DISEASE-ASSOCIATED MICROGLIA.** Cadiz MP, Haug KA, Fryer JD. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.
16. **EFFECT OF APOE ALLELIC ISOFORM AND AGE ON CAROTID ARTERY FUNCTION AND VASCULAR REACTIVITY.** Souders LJ, Hoxha B, Vallejo-Elias J, Jones C, Virden T, Jones TB, Eckman DM. Midwestern University; Arizona Alzheimer's Consortium.
17. **EFFECT OF APOE ϵ 4 STATUS ON PRECLINICAL COGNITION IN AUTOPSY CONFIRMED ALZHEIMER'S DISEASE.** Ng W, Malek-Ahmadi M, Auman B, Belden CM, Berger J, Horner C, Arch A, Sakhai S, Evans B, Glass M, Moorley NR, Davis KJ, Cline CD, Serrano GE, Beach TG, A Atri. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.
18. **EVALUATING TEMPLATE CREATION OF ADULT AND AGED BONNET MACAQUES.** Dieckhaus LA, McDermott KE, Gray DT, Comrie CJ, Hutchinson EB, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

19. **FIBRILLIN-1 MUTATION ACCELERATES CEREBROVASCULAR AGING AND INCREASES NEUROVASCULAR VULNERABILITY TO MILD TRAUMATIC BRAIN INJURY.** Curry T, Barrameda ME, Bromberg CE, Saber M, Rowe RK, Gonzales RJ, Esfandiarei M, Currier Thomas T. University of Arizona College of Medicine-Phoenix; University of Arizona; Midwestern University; Barrow Neurological Institute at Phoenix Children's Hospital; University of Colorado Boulder; Arizona Alzheimer's Consortium.
20. **FLORBETAPIR PET MEASUREMENTS OF AMYLOID PLAQUE DEPOSITION ARE MORE CLOSELY CORRELATED WITH CROSS-SECTIONAL AND LONGITUDINAL COGNITIVE AND CLINICAL MEASUREMENTS USING A WHITE MATTER REFERENCE REGION OF INTEREST.** Bhargava V, Wang M, Chen Y, Luo J, Weiner M, Landau S, Jagust W, Su Y, Reiman EM, Chen K. University of Arizona College of Medicine Phoenix; Banner Alzheimer's Institute; Arizona State University; Translational Genomics Research Institute; University of California San Francisco; University of California Berkeley; Arizona Alzheimer's Consortium.
21. **FUNCTIONAL CONNECTIVITY ACROSS VASCULAR SCALES IN ALZHEIMER'S DISEASE.** Keeling EG, Bergamino M, Sisco NJ, Raganathan S, Quarles CC, Prigatano GP, Stokes AM. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.
22. **GLYPHOSATE INFILTRATES THE BRAIN AND INCREASES PRO-INFLAMMATORY CYTOKINE TNFA: IMPLICATIONS FOR NEURODEGENERATIVE DISORDERS.** Winstone JK, Pathak KV, Winslow W, Piras IS, White J, Sharma R, Huentelman M, Pirrotte P, Velazquez R. Arizona State University; City of Hope Comprehensive Cancer Center; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.
23. **HYPOACTIVITY PREDICTS APOE-E4 CARRIER STATUS AND ELEVATED TRIGLYCERIDE LEVELS IN A HUMANIZED APOE MOUSE MODEL OF ALZHEIMER'S DISEASE.** McLean JW, Bhattra A, Vitali F, Raikes A, Wiegand JP, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.
24. **INTEGRATING TRANSCRANIAL MAGNETIC STIMULATION AND ELECTROENCEPHALOGRAPHY AS AN APPROACH FOR STUDYING MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE.** Hall JD, Green J, Chen AY, Chou Y-H. University of Arizona; Arizona Alzheimer's Consortium.
25. **INVESTIGATING AGE-RELATED CHANGES OF MPFC NEURAL RESPONSES TO VENTRAL HIPPOCAMPUS STIMULATION.** Srivathsa S, Vishwanath A, Cowen SL, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.
26. **INVESTIGATING THE CELLULAR MECHANISMS AND PHENOTYPIC EFFECTS OF THE APOE3 CHRISTCHURCH MUTATIONS IN AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE WITH ISOGENIC-BASED STEM CELL MODELS.** Frisch C, Brafman D. Arizona State University; Arizona Alzheimer's Consortium.
27. **INVESTIGATING THE PROTECTIVE MECHANISMS OF APOLIPOPROTEIN E2 (APOE2) IN MODULATING AMYLOID PRECURSOR PROTEIN (APP) PROCESSING.** Srinivasan G, Frisch C, Raman S, Brookhouser N, Brafman DA. Arizona State University; University of Arizona College of Medicine-Phoenix; Arizona Alzheimer's Consortium.

28. **LACK OF INTERACTION BETWEEN BDNF VAL66MET AND APOE E4 ON AMYLOID-PET, TAU-PET, HIPPOCAMPAL VOLUME, AND EPISODIC MEMORY IN COGNITIVELY UNIMPAIRED OLDER ADULTS.** Shaw A, Malek-Ahmadi M, Devadas V, Wang Q, Su Y, Reiman EM. University of Nottingham; Banner Alzheimer's Institute; Arizona State University; University of Arizona; Arizona Alzheimer's Consortium.
29. **LOOKING BACKWARD TO MOVE FORWARD: ON THE RELATIONSHIPS BETWEEN OVARIAN HORMONE LOSS, COGNITION, AND ANXIETY.** Lizik C, Bernaud V, Peña V, Andrew K, Mitbander A, Bimonte-Nelson H. Arizona State University; Arizona Alzheimer's Consortium.
30. **MIDDLE-AGED, GONADECTOMIZED RATS EXPOSED TO CHRONIC CORTICOSTERONE SHOW SEX DIFFERENCES IN HOW THEY RESPOND TO LONG-TERM 17BETA-ESTRADIOL TREATMENT ON SPATIAL WORKING MEMORY AND DEPRESSIVE-LIKE BEHAVIOR.** Potu SS, Peay DN, Eir CC, Whittaker KE, Bandin E, Conrad CD. Arizona State University; Arizona Alzheimer's Consortium.
31. **MRI SIGNATURES OF BRAIN AGE IN THE ALZHEIMER'S DISEASE CONTINUUM.** Shah J, Ghisays V, Chen Y, Luo J, Li B, Reiman EM, Chen K, Wu T, Su Y. Arizona State University; Mayo Clinic Arizona; Banner Alzheimer's Institute; University of Arizona; Arizona Alzheimer's Consortium.
32. **NEURODEGENERATION BIOMARKERS IN A PRECLINICAL MODEL OF VASCULAR DEMENTIA AND CLINICAL STUDIES OF HEART DISEASE INDIVIDUALS AT RISK FOR VASCULAR COGNITIVE IMPAIRMENT: EFFECTS OF TREATMENT WITH ANGIOTENSIN-(1-7).** Hoyer-Kimura C, Konhilas J, Ryan L, Hay M. University of Arizona; Arizona Alzheimer's Consortium.
33. **NEURODEGENERATIVE EFFECTS FOLLOWING A UNILATERAL TRAUMATIC BRAIN INJURY.** Bjorklund GR, Wong J, Brafman D, Stabenfeldt SE, Bowser R. Arizona State University; Barrow Neurological Institute; Arizona Alzheimer's Consortium.
34. **NEUROINFLAMMATORY PROFILES OF THE HUMAN FEMALE BRAIN AT MIDLIFE RESEMBLES THE HUMAN MALE LATE-LIFE ALZHEIMER'S BRAIN.** Delatorre N, Van Rossum H, Mishra A, Padilla-Rodriguez M, Rodgers K, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.
35. **NOISE2DWI: A SELF-SUPERVISED DEEP LEARNING METHOD FOR ACCELERATED DIFFUSION TENSOR IMAGING.** Martin P, Altbach M, Bilgin A. University of Arizona; Arizona Alzheimer's Consortium.
36. **NOVEL ALLOSTERIC NAD ENHANCEMENT TO SUPPORT NEURAL RESILIENCE IN ADRD.** Krider IS, Ratia KM, Shen Z, Laham M, Ackerman-Berrier M, Penton C, Knowles NG, Reddy MS, Reddy VG, Xiong R, Fu J, Thatcher GRJ. University of Arizona; University of Illinois at Chicago; Arizona Alzheimer's Consortium.
37. **PROGRANULIN PROCESSING AND GROWTH RESPONSE IN SW13 CELLS: POTENTIAL LINKS TO LYSOSOMAL FUNCTION AND NEURODEGENERATIVE DISEASE.** Biparva P, Pascual AS, Montgomery MR, Leyva KJ, Hull EE. Midwestern University; Oklahoma State University; Arizona Alzheimer's Consortium.

38. **REAL-WORLD GOAL SETTING AND FOLLOW THROUGH IN YOUNG AND OLDER ADULTS.** Lauren E. Cruz LE, Christopher X. Griffith CX, Cegavske C, Burns H, Andrews-Hanna JR, Grilli MD. University of Arizona; Arizona Alzheimer's Consortium.
39. **STATIN RESPONDER ANALYSIS FOR PRECISION PREVENTION OF ALZHEIMER'S DISEASE.** Torrandell-Haro G, Branigan GL, Rodgers KE, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.
40. **SYSTOLIC BLOOD PRESSURE AND LONGITUDINAL WHITE MATTER HYPERINTENSITY DATA FROM TWO STUDIES TO INFORM THE DESIGN OF AN ANTI-HYPERTENSIVE PREVENTION TRIAL IN MIDDLE-AGED ADULTS.** Nichols JB, Chen Y, Chen K, Su Y, Tsai P, Reiman EM, Alexander RC, Tariot PN, Pruzin JJ. Banner Alzheimer's Institute; Midwestern University; Arizona State University; University of Arizona; Arizona Alzheimer's Consortium.
41. **TARGET PRODUCT PROFILE AND DESIGN PATH TOWARD DYR533: A SMALL MOLECULE TOWARD AD AND IND-ENABLING STUDIES.** Rokey S, Foley C, Shaw Y, Bartholomew SK, Winslow W, Dunckley T, Velazquez R, Hulme C. University of Arizona; Arizona State University; Illuminos Therapeutics, LLC; Arizona Alzheimer's Consortium.
42. **TDP-43 PROTEINOPATHY INDUCED TRANSCRIPTIONAL ALTERATIONS IN ALZHEIMER'S DISEASE.** Pevey R, Moore S, Antone J, Alsop E, Hall W, Preller K, Mufson E, van Keuren-Jenson K, Sattler R. Barrow Neurological Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.
43. **THE AUTOBIOGRAPHICAL INTERVIEW ADMINISTERED DURING THE 2020 SARS COV2/CORONAVIRUS PANDEMIC VIA ZOOM-BASED FORMAT.** Hernandez DA, Griffith C, Deffner AM, Andrews-Hanna J, Grilli MD. University of Arizona; Arizona Alzheimer's Consortium.
44. **THE EMERGING ROLE OF ABERRANT TRANSFORMING GROWTH FACTOR- β (BETA) SIGNALING IN BRAIN PATHOPHYSIOLOGY.** Curtin L, Curry T, Bromberg C, Krishna G, Currier Thomas T. University of Arizona College of Medicine Phoenix; Phoenix Children's Hospital; Midwestern University; Arizona Alzheimer's Consortium.
45. **THE IMPACT OF CONTEXT ON MEMORY FOR SHORT STORIES AMONG OLDER AND YOUNGER ADULTS.** Palmer JM, Guareña LA, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.
46. **THE IMPACT OF COVID-19 RESPIRATORY SYMPTOMS & LEVELS OF NFL AMONG OLDER ADULTS ON COGNITIVE PERFORMANCE.** Galdamez-Avila A, Palmer JM, Lee Ryan L. University of Arizona; Arizona Alzheimer's Consortium.
47. **THE LONG AND WINDING ROAD: DO DIFFERENT PATHWAYS TO HYSTERECTOMY LEAD TO THE SAME COGNITIVE DESTINATION?** Pastor J, Bernaud V, Bandin E, Dyer C, Mayer L, Hanson T, Ruhland A, Bimonte-Nelson HA. Arizona State University; FYXX Foundation; Arizona Alzheimer's Consortium.
48. **THE NOVEL DYR533 DYRK1A INHIBITOR REDUCES AD-LIKE PATHOGENIES IN THE 3XTG-AD MOUSE MODEL OF ALZHEIMER'S DISEASE.** Bartholomew SK, Winslow W, Shaw Y, Rokey S, Foley C, Hulme C, Dunckley T, Velazquez R. Arizona State University; University of Arizona; Arizona Alzheimer's Consortium.

49. **“THROUGH ALZHEIMER’S EYES”: A VIRTUAL PILOT INTERVENTION FOR CAREGIVERS OF PEOPLE WITH DEMENTIA.** Gómez-Morales A, Carll P, Glinka A, Gonzalez-Pyles S, Perez S, Coon DW. Arizona State University; Arizona Alzheimer’s Consortium.
50. **TRANSFER LEARNING BASED DEEP ENCODER DECODER NETWORK FOR AMYLOID PET HARMONIZATION WITH SMALL DATASETS.** Shah J, Chen K, Reiman EM, Li B, Wu T, Su Y. Arizona State University; Mayo Clinic Arizona; Banner Alzheimer’s Institute; University of Arizona; Arizona Alzheimer’s Consortium.
51. **TRANSLATION OF POST MORTEM MRI METHODS TO CLINICAL SCANNER PROTOCOLS FOR THE DETECTION OF MICROSTRUCTURAL PATHOLOGY IN ALZHEIMER’S DISEASE.** Comrie CJ, Chen NK, Johnson K, Hutchinson EB. University of Arizona; Arizona Alzheimer’s Consortium.
52. **TRANSLATIONAL POTENTIAL OF JAX HUMANIZED APOE MICE: PERIPHERAL INTERFERON GAMMA INDUCES SYSTEMIC IMMUNO-METABOLIC DYSFUNCTION.** Van Rossum H, Delatorre N, Mishra A, Bhattra A, Raikes A, Rodgers K, Brinton RD. University of Arizona; Arizona Alzheimer’s Consortium.
53. **TRANSLATIONAL POTENTIAL OF JAX HUMANIZED-APOE MICE: SEX DIFFERENCES IN BIOENERGETIC FUNCTION IN BRAIN.** Cortes-Flores H, Altemus J, Wiegand JP, Brinton RD. University of Arizona; Arizona Alzheimer’s Consortium.
54. **TRANSLATIONAL POTENTIAL OF THE JAX HUMANIZED APOE AD MOUSE MODEL: METABOLISM AND BODY IN MICE EQUIVALENT TO 60-70YR OLD HUMAN.** Bhattra A, McLean W, Raikes A, Wiegand JP, Skopp S, Howison C, Galons JP, Brinton RD. University of Arizona; Arizona Alzheimer’s Consortium.
55. **TREATMENT FOR PHONOLOGICAL TEXT AGRAPHIA IN LOGOPENIC VARIANT PRIMARY PROGRESSIVE APHASIA: A HETEROGENEOUS CASE SERIES.** Nickels KV, Beeson P, Rising K, Jebahi F, Frazie NJ, Kielar A. University of Arizona; Arizona Alzheimer’s Consortium.
56. **USING FREE-WATER DIFFUSION TENSOR IMAGING TO IDENTIFY MICROSTRUCTURAL DIFFERENCES IN A PRECLINICAL MODEL OF ALZHEIMER’S DISEASE.** Nelson MR, Bergamino M, Numani A, Scarpelli M, Healey D, Fuentes A, Turner G, Oddo S, Stokes AM. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer’s Consortium
57. **VALIDATION OF A CLINICAL SCALE FOR DEFINING RBD SEVERITY IN PARTICIPANTS OF THE NORTH AMERICAN PRODROMAL SYNUCLEINOPATHY (NAPS) CONSORTIUM.** Buscescu A, Choudhury P, Lee-Iannotti JK, Rangan P, Shprecher D, Fantini ML, Lim M, Elliott J, Avidan A, Huddleston D, Bliwise D, Howell M, Schenck C, Criswell S, During E, Mignot E, McLeland J, Pelletier A, Gagnon J, Forsberg L, Fields J, St. Louis E, Videnovic A, Ju Y, Boeve B, Postuma R. University of Arizona College of Medicine-Phoenix; Banner Sun Health Research Institute; Banner University Medical Center; Le Centre Hospitalier Universitaire; Oregon Health & Science University; Ohio Health; David Geffen School of Medicine at UCLA; Emory University; University of Minnesota; Minnesota Regional Sleep Disorders Center; Washington University; Stanford University; Stanford Center for Sleep Sciences and Medicine; Montreal General Hospital; Center for Advanced Research in Sleep Medicine; Mayo Clinic; MGH Neurological Clinical Research Institute.

58. **VOLUMETRIC MRI ANALYSIS OF RODENT BRAINS AS A FUNCTION OF AGE AND COGNITION.** Do L, Zempare MA, Bernstein AS, Bharadwaj PK, Carey N, Nguyen C, Alexander GE, Barnes CA, Trouard TP. University of Arizona; Arizona Alzheimer's Consortium.
59. **VOLUMETRIC PREDICTORS OF EXECUTIVE FUNCTION IN COGNITIVELY UNIMPAIRED OLDER ADULTS.** Andrew K, Malek-Ahmadi M. Arizona State University; Banner Alzheimer's Institute; University of Arizona College of Medicine-Phoenix; Arizona Alzheimer's Consortium.

Poster Presentations

60. **A GENOME-WIDE SCREEN FOR HUMAN PROTEINS THAT AFFECT AMYLOID BETA PEPTIDE PRODUCTION BY GAMMA SECRETASE USING A YEAST GENETIC SYSTEM.** Adland E, Lewis KN, Sorenson K, Carpenter R, Chen C, Shumaker E, Solomon C, Pham C, Bae NS, Swanson MJ. Northwestern University; Arizona Alzheimer's Consortium.
61. **A HIGH-RESOLUTION 3D RECONSTRUCTION OF THE LOCUS COERULEUS IN AGED MACAQUES: A COMBINED MRI, NISSL AND ANTI-TYROSINE HYDROXYLASE (TH) IMMUNOFLOUORESCENCE STUDY.** Sinakevitch I, McDermott K, Khattab SO, Gray DT, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.
62. **ABERRANT FATTY ACID DEGRADATION BY ASTROCYTIC MITOCHONDRIA AS A MECHANISM OF BRAIN LIPID DROPLET ACCUMULATION AND LIPID DYSHOMEOSTASIS.** Qi G, Mi Y, Jin Y, Gu H, Yin F. University of Arizona; Florida International University; Arizona Alzheimer's Consortium.
63. **ACCELERATED MIDLIFE AGING IN hAPOE ϵ 4/4 FEMALES.** Wang T, Mao Z, Delatorre N, Wiegand JP, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.
64. **AGE- AND AGING-WITH-INJURY-RELATED TEMPORAL MICROGLIAL MORPHOLOGICAL PROFILES INDICATE UNIQUE PATHOLOGICAL PROCESSES IN BEHAVIORALLY RELEVANT CIRCUIT RELAYS.** Krishna G, Sanghadia C, Sabetta Z, Rajaboina B, Adelson PD, Thomas TC. University of Arizona College of Medicine-Phoenix; Barrow Neurological Institute at Phoenix Children's Hospital; Phoenix VA Healthcare System; University of Arizona; Arizona State University; Arizona Alzheimer's Consortium.
65. **AGE-RELATED CHANGES IN PERFORMANCE ON THE FRONTAL CORTEX-DEPENDENT TEMPORAL ORDER MEMORY TASK.** Guswiler O, Khattab S, Bohne K, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.
66. **APOE AND CLU COOPERATIVELY PROMOTE AMYLOID FORMATION.** Ding Z, Haug KA, Fryer JD. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.
67. **ASSESSMENT OF FINGER TAPPING ABNORMALITIES IN OLDER ADULTS WITH MEMORY COMPLAINTS.** McElvoque MM, Steffes L, Burke A, Stokes A, Prigatano GP. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

68. **ASSOCIATION OF APOE E4 WITH DECREASED EMOTIONAL PRECISION OF WORD USE IN NON-DEMENTED OLDER ADULTS.** Stoica T, Grilli MD, Andrews-Hanna J. University of Arizona; Arizona Alzheimer's Consortium.
69. **ASTROCYTIC MITOCHONDRIAL DYSFUNCTION INDUCES NEURODEGENERATION THAT RESEMBLES ALZHEIMER'S DISEASE.** Mi Y, Qi G, Vitali F, Shang Y, Raikes AC, Wang T, Brinton RD, Yin F. University of Arizona; Arizona Alzheimer's Consortium.
70. **BLOOD-BASED PROTEIN VARIANT BIOMARKER PANEL FOR EARLY DIAGNOSIS OF ALZHEIMER'S DISEASE.** Schulz P, Cho HJ, Venkataraman L, Sierks MR. Arizona State University; Arizona Alzheimer's Consortium.
71. **CAREPLACE: AN INNOVATIVE COMMUNITY BASED CARE COORDINATION PROGRAM TO ADDRESS UNMET CAREGIVER NEEDS, A PILOT STUDY.** Buchanan BL, Reynolds L, Bordenave E. AT Still University.
72. **CAREPRO SPANISH: A VIRTUAL INTERVENTION FOR THE LATINO COMMUNITY.** Gonzalez-Pyles S, Covarrubias A, Carbajal B, Carbajal L, Córdova L, Pérez S, Manzo A, Coon DW. Arizona State University; Arizona Alzheimer's Consortium.
73. **CASE REPORT: A SEVERE REACTION TO MRNA SARS-COV-2 VACCINE BOOSTER IN AN APOE-EPSILON 4 CARRIER WITH MILD ALZHEIMER'S DISEASE RECEIVING ADUCANUMAB IN A CLINICAL TRIAL.** Restifo LL, Erickson RP. University of Arizona College of Medicine-Tucson; University of Arizona; Arizona Alzheimer's Consortium.
74. **CEREBRAL MICROVASCULAR DYSFUNCTION IN 5X-FAD MICE: ROLE OF BIOLOGICAL SEX, BK CHANNEL ACTIVITY AND OXIDATIVE STRESS.** Silva JF, Savu A, Polk FD, Kath AM, Pires PW. University of Arizona College of Medicine, Tucson; Arizona Alzheimer's Consortium.
75. **CHARACTERIZATION OF BACTERIAL 16S RRNA GENE SEQUENCES EXTRACTED FROM POST-MORTEM BRAIN TISSUE OF AD PATIENTS AND CONTROLS.** Jentarra G, Wilkey B, Chu P, Gonzalez F, Rogers A, Vallejo J, Jones D, Lynch L, Jones TB. Midwestern University; Arizona Alzheimer's Consortium.
76. **CHRONIC COGNITIVE AND CEREBROVASCULAR FUNCTION FOLLOWING MILD TRAUMATIC BRAIN INJURY IN RATS.** Griffiths DR, Law LM, Young C, Fuentes A, Truran S, Karamanova N, Bell LC, Turner G, Emerson H, Mastroeni D, Gonzales RJ, Reaven P, Quarles CC, Migrino RQ, Lifshitz J. Phoenix VA Health Care System; University of Arizona College of Medicine – Phoenix; Barrow Neurological Institute at Phoenix Children's Hospital; Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.
77. **CLINICAL PREDICTORS OF ALZHEIMER'S DISEASE DEVELOPMENT IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT USING SYNTHETIC DATA DERIVED FROM VETERANS AFFAIRS ELECTRONIC HEALTH RECORDS.** Irwin CM, Tjandra D, Aggarwal V, Hu C, Giordani B, Wiens J, Migrino RQ. Phoenix VA Healthcare System; The University of Arizona College of Medicine – Phoenix; University of Michigan; MD Clone; Arizona Alzheimer's Consortium.

78. **COGNITIVE HETEROGENEITY AND RISK OF PROGRESSION IN DATA-DRIVEN SUBTLE COGNITIVE DECLINE PHENOTYPES.** Edmonds EC, Thomas KR, Bangen KJ, Weigand AJ, Ortiz G, Walker KS, Salmon DP, Bondi MW. Banner Alzheimer's Institute; University of Arizona; University of California, San Diego; VA San Diego Healthcare System; San Diego State University; Arizona Alzheimer's Consortium.
79. **CRITICAL PATH FOR ALZHEIMER'S DISEASE (CPAD) CONSORTIUM: PRE-COMPETITIVE COLLABORATION TO ACCELERATE AND DE-RISK DRUG DEVELOPMENT IN ALZHEIMER'S DISEASE.** Sivakumaran S, Cullen N, Priest E, Lau C, Karten Y. Critical Path Institute; Arizona Alzheimer's Consortium.
80. **DEEP LEARNING APPLICATION IN RETINAL IMAGING CLASSIFICATION OF ALZHEIMER'S DISEASE.** Dumitrascu OM, Zhu W, Qiu P, Nandakumar K, Wang Y. Mayo Clinic Arizona; Arizona State University; Washington University.
81. **DEMENTIA-RELATED ANXIETY: WHAT'S THE WORRY?** Maxfield M, Peckham A, James D. Arizona State University; University of South Alabama; Arizona Alzheimer's Consortium.
82. **DIETARY CHOLINE DEFICIENCY THROUGHOUT ADULTHOOD INDUCES SYSTEMS-WIDE DYSFUNCTION AND INCREASES ALZHEIMER'S DISEASE RISK ACROSS SEVERAL PATHOGENIC AXES.** Judd JM, Dave N, Decker A, Winslow W, Sarette P, Espinosa OV, Sandler J, Bilal A, Tallino S, McDonough I, Winstone JK, Blackwood EA, Glembotski C, Karr T, Velazquez R. Arizona State University; University of Arizona College of Medicine–Phoenix; Arizona Alzheimer's Consortium.
83. **EARLY-STAGE PARTNERS IN CARE (EPIC) LIVING ALONE: A VIRTUAL PILOT FOR PEOPLE LIVING ALONE WITH EARLY-STAGE MEMORY PROBLEMS.** Glinka A, Gonzalez-Pyles S, Carll P, Perez, S, Coon DW. Arizona State University; Arizona Alzheimer's Consortium.
84. **EFFECTS OF MINDFUL AWARENESS PRACTICE (MAP) INTERVENTION ON SUBCLINICAL DEPRESSIVE AND ANXIETY SYMPTOMS AND GENERAL COGNITIVE FUNCTION IN OLDER ADULTS WITH MILD COGNITIVE IMPAIRMENT: A 5-YEAR FOLLOW-UP OF THE MAP-RANDOMIZED CONTROLLED TRIAL.** Ng TKS, Tan XR, Chen ACC, Lei F, Lu Y, Yu F, Kua EH, Mahendran R. Arizona State University; National University of Singapore; Singapore Institute of Technology; Shandong University; National University Hospital, Singapore; Arizona Alzheimer's Consortium.
85. **EXAMINING THE CELLULAR DISTRIBUTION OF TELOMERE PROTEIN RAP1 DURING OXIDATIVE STRESS.** Whetzel A, Bandara D, Lewis KN, Swanson MJ, Bae NS. Northwestern University; Arizona Alzheimer's Consortium.
86. **EXERCISE TRAINING PREVENTS THE LOSS OF WALL THICKNESS AND LOWERS EXPRESSION OF ALZHEIMER'S RELATED PROTEINS IN 3XTG MOUSE JEJUNUM.** Al-Nakkash L, Mason D, Ismail N, Bowman T, Ahlert J, Rubin M, Smith E, Rosander A, Broderick TL. Northwestern University; Arizona Alzheimer's Consortium.
87. **GLYCOSYLATED HORMONES AS BRAIN-PENETRANT NEUROPROTECTIVE DRUGS.** Polt R, Falk T, Streicher J, Heien ML, Apostol CR, Szabo L, Alabsi W, Tanguturi P. University of Arizona; Arizona Alzheimer's Consortium.

88. **IMPROVED PREDICTION OF THE MEASUREMENTS OF TAU AND BETA-AMYLOID BURDEN USING HIPPOCAMPAL SURFACE MULTIVARIATE MORPHOMETRY STATISTICS AND SPARSE.** Wu J, Zhu W, Gui J, Lepore N, Reiman EM, Caselli RJ, Thompson PM, Chen K, Su Y, Wang Y. Arizona State University; Banner Alzheimer's Institute; University of Arizona; School of Cyber Science and Engineering Southeast University; Children's Hospital Los Angeles; Mayo Clinic Arizona; University of Southern California; Arizona Alzheimer's Consortium.
89. **INCREASED SPATIAL EXTENT OF CEREBRAL TAU PET ELEVATIONS IN FORMER NFL AND COLLEGE FOOTBALL PLAYERS FROM THE DIAGNOSE CTE RESEARCH PROJECT.** Chen K, Reiman EM, Luo J, Protas H, Cummings JL, Shenton ME, Stern RA, Su Y for the DIAGNOSE CTE Research Project. Banner Alzheimer's Institute; Arizona State University; University of Arizona; Translational Genomics Research Institute; Boston University School of Medicine; Brigham and Women's Hospital; University of Nevada; Arizona Alzheimer's Consortium.
90. **INVESTIGATING BIOLOGICAL PATHWAYS UNDERPINNING THE LONGITUDINAL ASSOCIATION BETWEEN LONELINESS AND COGNITIVE IMPAIRMENT.** Yu K, Ng TKS. University of Southern California; Arizona State University; National University of Singapore; Arizona Alzheimer's Consortium.
91. **INVESTIGATING THE EFFECT OF TAU DEPOSITION AND APOE ON HIPPOCAMPAL MORPHOMETRY IN ALZHEIMER'S DISEASE: A FEDERATED CHOW TEST MODEL.** Wu J, Su Y, Reiman EM, Caselli RJ, Chen K, Thompson PM, Wang J, Wang Y. Arizona State University; Banner Alzheimer's Institute; University of Arizona; Mayo Clinic, Scottsdale; University of Southern California; Arizona Alzheimer's Consortium.
92. **ISCHEMIC OUTCOME IN YOUNG AND ADULT MALE AND FEMALE OFFSPRING AFTER MATERNAL DEFICIENCIES IN ONE-CARBON METABOLITES DURING PREGNANCY AND LACTATION.** Clementson M, Hurley L, Jauhal J, Coonrod S, Bennett C, Pull K, Pascual A, Wasek B, Bottiglieri T, Malysheva O, Caudill MA, Jadavji NM. Midwestern University; Baylor Scott & White Research Institute; Cornell University; Carleton University; Arizona Alzheimer's Consortium.
93. **MICROBIAL AND PROTEOMIC ANALYSES REVEALED SIGNIFICANT CHANGES IN MICROBIOME COMPOSITION AND DEFENSE RESPONSE IN ALZHEIMER'S GUT.** Mastroeni D, Krajmalnik-Brown R, Cheng Q, Karr T. Arizona State University; Arizona Alzheimer's Consortium.
94. **MICROSTRUCTURAL MR MARKERS OF ALZHEIMER'S DISEASE PATHOLOGY IN POST-MORTEM HUMAN TEMPORAL LOBE.** Comrie CJ, Dieckhaus LA, Beach TG, Serrano GE, Hutchinson EB. University of Arizona; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.
95. **MODERATING EFFECT OF COGNITIVE RESERVE ON BRAIN INTEGRITY AND COGNITIVE PERFORMANCE.** Nelson ME, Veal BM, Andel R, Martinkova J, Veverova K, Horakova H, Nedelska Z, Laczó J, Vyhnalek M, Hort J. University of South Florida; Charles University and Motol University Hospital, Prague, Czech Republic; St. Anne's University Hospital Brno, Czech Republic.

96. **MULTI-OMICS ANALYSIS SUGGESTS INCREASED EXOCYTIC PROCESSES IN THE BRAINS OF PATIENTS WITH TRISOMY-21 AND ALZHEIMER'S DISEASE.** Piras IS, Beres S, Hudson S, Johnson M, Wright S, Tallino S, Head E, Huentelman M, Velazquez R. Translational Genomics Research Institute; University of California, Irvine; Arizona State University; Arizona Alzheimer's Consortium.
97. **NETWORK-BASED GENOME ANALYSIS OF COGNITIVE IMPAIRMENT IN A SOUTH AMERICAN INDIGENOUS POPULATION.** Garcia AR, Lu YK, Gatz M, Mack WJ, Chui HC, Law M, Barisano G, Eid Rodriguez D, Gutierrez RQ, Copajira Adrian J, Bani Cuata J, Sutherland ML, Sutherland JD, Kraft TS, Borenstein AR, Irimia A, Thomas GS, Thompson RC, Miyamoto MI, Michalik DE, Wann LS, Walters EE, Allam A, Rowan CJ, Cummings DK, Highland HM, North KE, Finch CE, Stieglitz J, Gurven MD, Trumble BC, Kaplan H, Buetow K. Arizona State University; Phoenix Children's Hospital; University of Arizona; University of Southern California; Monash University; San Simon University; Tsimane Health and Life History Project; MemorialCare Health Systems; University of Utah; University of California, San Diego; University of California, Irvine; University of Missouri-Kansas City; Providence Health; University of New Mexico; Al-Azhar University; Renown Institute for Heart and Vascular Health; Chapman University; University of North Carolina at Chapel Hill; Université Toulouse 1 Capitole; University of California, Santa Barbara.
98. **NEUROIMAGING CORRELATES OF FUNCTIONAL MOTOR CHANGES IN COGNITIVELY IMPAIRED COHORTS.** Bergamino M, Keeling E, Schaefer S, Burke A, Prigatano G, Stokes A. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.
99. **NOVEL IMAGING MARKERS FOR ALTERED CEREBROVASCULAR MORPHOLOGY IN AGING AND ALZHEIMER'S DISEASE.** Deshpande A, Elliott J, Laksari K. University of Arizona; Arizona Alzheimer's Consortium.
100. **OLDER ADULT WILLINGNESS TO ENROLL IN AD-FOCUS RECRUITMENT REGISTRIES AND TO PARTICIPATE IN REGISTRY-SPECIFIC ACTIVITIES: A NATIONALLY REPRESENTATIVE SAMPLE OF OLDER ADULTS IN THE UNITED STATES.** Bleakley A, Maloney E, Hennessy M, Karlawish J, Harkins K, Nosheny R, Langbaum JB. University of Delaware; University of Pennsylvania; University of California San Francisco; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.
101. **PERSONAL MENTAL TIME TRAVEL MAY BE AN IMPORTANT COGNITIVE MECHANISM BEHIND ALZHEIMER'S DISEASE RISK-RELATED REDUCTIONS IN EVENT CONSTRUCTION EPISODIC SPECIFICITY.** Deffner AM, Stoica T, Thayer SC, Andrews-Hanna J, Grilli MD. University of Arizona; Arizona Alzheimer's Consortium.
102. **PLASMA NEUROFILAMENT LIGHT CHAIN IN COGNITIVELY UNIMPAIRED LATE MIDDLE-AGED & OLDER ADULT APOE E4 HOMOZYGOTES, HETEROZYGOTES, & NON-CARRIERS FROM THE ARIZONA APOE COHORT.** Ghisays V, Su Y, Malek-Ahmadi MH, Jansen WJ, Protas HD, Chen Y, Lee W, Luo J, Bauer RJ, Chen K, Caselli RJ, Zetterberg H, Blennow K, Reiman EM. Banner Alzheimer's Institute; Mayo Clinic, Scottsdale; Sahlgrenska University Hospital; University of Gothenburg; University College London; Hong Kong Center for Neurodegenerative Diseases; Arizona State University; University of Arizona; Arizona Alzheimer's Consortium.

103. **POSTNATAL CHEMOPHENOTYPIC NEURONAL ALTERATIONS IN THE FRONTAL CORTEX, HIPPOCAMPUS AND CEREBELLUM IN DOWN SYNDROME.** Perez SE, Moreno DG, Utagawa EG, Miquel JC, Arva NC, Schafernak KT, Mufson EJ. Barrow Neurological Institute; Ann & Robert H. Lurie Children's Hospital of Chicago; Phoenix Children's Hospital; Arizona Alzheimer's Consortium.
104. **PREDICTING BRAIN AMYLOIDOSIS WITH PLASMA B-AMYLOID42/40 AND MRI-BASED MORPHOMETRY FEATURES.** Wu J, Su Y, Thompson PM, Reiman EM, Caselli RJ, Chen K, Wang Y. Arizona State University; Banner Alzheimer's Institute; University of Southern California; University of Arizona; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.
105. **PRELIMINARY BASELINE BRAIN CORRELATES OF ACCELERATED VISUAL MEMORY DECLINE IN MIDDLE-AGE AND OLDER ADULTS WITH AUTISM: THE CASE FOR HIPPOCAMPAL FREE-WATER.** Walsh MJM, Ofori E, Pagni BA, Chen K, Sullivan G, Braden BB. Arizona State University; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.
106. **RECRUITED COHORT DIFFERENCES BETWEEN TWO VERSIONS OF A WEB-BASED STUDY OF COGNITION.** Huentelman M, De Both M, Johnson M, Hoscheidt S, Irwin K, The Precision Aging Network Research Team, Ryan L. Translational Genomics Research Institute; Precision Aging Network; University of Arizona; Arizona Alzheimer's Consortium.
107. **REPRODUCTIVE HEALTH DATA AND ITS RELATIONSHIP TO BASELINE BRAIN IMAGING AND COGNITIVE MEASUREMENTS IN COGNITIVELY UNIMPAIRED FEMALE PSEN1 E280A MUTATION CARRIERS AND NON-CARRIERS FROM THE API ADAD TRIAL.** Ghisays V, Vila-Castelar C, Giraldo-Chica M, Acosta-Baena N, Protas HD, Malek-Ahmadi MH, Chen Y, Luo J, Lee W, Bocanegra Y, Muñoz C, Herrera K, Hu N, Sink KM, Clayton D, Alvarez S, Langbaum JB, Chen K, Su Y, Tariot PN, Quiroz YT, Lopera F, Reiman EM, Rios-Romenets S, API ADAD Colombia Trial Group. Banner Alzheimer's Institute; Universidad de Antioquia; Massachusetts General Hospital, Harvard Medical School; Genentech Inc.; Hospital Pablo Tobón Uribe; Arizona State University; University of Arizona; Arizona Alzheimer's Consortium.
108. **SALUTARY BIO-PSYCHO-SOCIAL EFFECTS OF NATURE AWARENESS INTERVENTION ON OLDER ADULTS WITH LONG-COVID AND BRAIN FOG: A PILOT RANDOMIZED CONTROLLED TRIAL.** Ng TKS, Tanner L, Thomas R, Wu S, Lim E, Maxfield M, Larkey L. Arizona State University; National University of Singapore; Arizona Alzheimer's Consortium.
109. **SEROTONIN REUPTAKE INHIBITORS ARE ASSOCIATED WITH LESS AMYLOID-B BURDEN SPATIAL EXTENT IN MILITARY VETERANS WITH ONLY PTSD, BUT NOT WITH TBI OR COMORBID PTSD/TBI: PRELIMINARY PET FINDINGS FROM ADNI-DOD PROJECT.** Chen K, Goradia DD, Chen Y, Luo J, Devadas V, Jagust W, Mackin S, Su Y, Landau S, Weiner M, Reiman EM. Banner Alzheimer's Institute; Arizona State University; University of Arizona; UC Berkeley; UC San Francisco; Veterans Affairs Medical Center; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

110. **SEX- AND APOE-SPECIFIC TRANSCRIPTOMIC SIGNATURES IN ALZHEIMER'S DISEASE: AN AZ-ADRC-RESEARCH EDUCATION SCHOLARS TEAM SCIENCE PROJECT.** Vitali F, Raikes A, Hernandez GD, Yin F. University of Arizona; University of Arizona College of Medicine Tucson; Arizona Alzheimer's Consortium.
111. **SEX-DEPENDENT CHANGES IN LEARNING AND FLEXIBILITY DURING AGING IN MICE.** Lyle T, Truong V, Bowser S, Bimonte-Nelson H, Verpeut J. Arizona State University; Arizona Alzheimer's Consortium.
112. **SEX-SPECIFIC GENE EXPRESSION OBSERVED IN HUMAN DEMENTIA WITH LEWY BODIES (DLB).** Olney KC, Rabichow BE, Ross OA, Chang R, Fryer JD. Mayo Clinic, Scottsdale; Arizona State University; Mayo Clinic Graduate School of Biomedical Sciences; Mayo Clinic, Jacksonville; University of Arizona; Arizona Alzheimer's Consortium.
113. **SHALLOW SHOTGUN METAGENOMIC SEQUENCING OF THE GUT MICROBIOTA THROUGHOUT IN 3XTG-AD MICE REVEALS THE LONGITUDINAL DYNAMICS OF GUT MICROBIAL SPECIES AND STRAINS.** Borsom EM, Conn KA, Testo G, Hirsch AH, Orsini GM, Jaramillo SA, Lee, Caporaso JG, Cope EK. Northern Arizona University; Translational Genomics North; Arizona Alzheimer's Consortium.
114. **SIMULTANEOUSLY DEVELOPING INTERVENTIONS FOR LOW-, MIDDLE-, AND HIGH-INCOME SETTINGS: CONSIDERATIONS AND OPPORTUNITIES.** Baker ZG, Nkimbeng M, Cuevas PEG, Quiñones AR, Kang HK, Gaugler JE, Hinton L, Gitlin LN, Shippee TP. Arizona State University; University of Minnesota; Centro Escolar University; Oregon Health and Science University; Chitkara University; University of California – Davis; Drexel University; Arizona Alzheimer's Consortium.
115. **SINGLE NUCLEI TRANSCRIPTOMIC PROFILES OF C9ORF72 PATIENTS WITH COGNITIVE SYMPTOMS SPANNING THE ALS-FTD SPECTRUM.** Gittings LM, Alsop EB, Antone J, Singer M, Sattler R, van Keuren-Jensen K. Barrow Neurological Institute; Translational Genomics Research Institute; Arizona State University; Arizona Alzheimer's Consortium.
116. **THE DATA MANAGEMENT AND STATISTICAL CORE (DMSC) AND THE NATIONAL ALZHEIMER'S COORDINATING CENTER'S (NACC) "DATA FRONT DOOR" (DFD) COLLABORATION.** Amador R, Bauer III RJ, Parizek D, Saner D. Banner Alzheimer's Institute; University of Arizona; Arizona Alzheimer's Consortium.
117. **THE LONG-TERM EFFECTS OF INTERMITTENT FASTING ON SIGNS OF AGING IN SENESCENCE ACCELERATED MOUSE-PRONE 8 (SAMP8) MICE.** Meyers A, Kargari S, Crisan N, Mody A, Shim M. Arizona College of Osteopathic Medicine; Midwestern University.
118. **THE TELOMERE PROTECTION PROTEIN RAP1 AND THE EPSILON ISOFORM OF GLIAL FIBRILLARY ACIDIC PROTEIN ACTIVATE GAMMA-SECRETASE ACTIVITY.** Lewis KN, Carpenter R, Bae NS, Swanson MJ. Midwestern University; Arizona Alzheimer's Consortium.
119. **TRAILBLAZER-ALZ 3 TRIAL DESIGN AND RATIONALE.** Tariot PN, Reiman EM, Alexander RC, Langbaum JB, Holdridge K, Ferguson MB, Yaari R, Sims JR, Zappone CA. Banner Alzheimer's Institute; Arizona State University; University of Arizona; Eli Lilly and Company; Arizona Alzheimer's Consortium.

120. **TRANSLATIONAL POTENTIAL OF JAX HUMANIZED APOE MICE: HIPPOCAMPAL VOLUME DECLINE IN AGED MOUSE EQUIVALENT OF 60-70 YR HUMAN.** Raikes AC, Bhattarai A, McLean JW, Wiegand JPL, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.
121. **TRANSLATIONAL POTENTIAL OF JAX HUMANIZED APOE MICE: TRAJECTORIES OF RESILIENT VERSUS SUSCEPTIBLE AGING BY SEX AND WEIGHT.** Vitali F, Wiegand JP, Tucker A, Brinton RD. University of Arizona; Brunel University London; Arizona Alzheimer's Consortium.
122. **TRAUMATIC BRAIN INJURY GENERATES ALZHEIMER'S DISEASE RELATED PROTEIN VARIANTS IN MOUSE MODEL BRAIN TISSUE.** Panayi N, Schulz P, He P, Rowe RK, Sierks MR. Arizona State University; University of Colorado Boulder; Arizona Alzheimer's Consortium.
123. **ABNORMAL GLIAL TDP43 INCLUSIONS IN A DEMENTIA CASE.** Tremblay C, Intorcchia AJ, Mesch K, Walker JE, Arce RA, Qiji SH, Borja CI, Cline MP, Hemmingsen SJ, Aslam S, Mariner M, Suszczewicz KE, Krupp A, Martinez K, McHattie R, Stewart A, Beh ST, Beach TG, Serrano GE. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.
124. **ALZHEIMER'S DISEASE NEUROPATHOLOGICAL COMORBIDITIES ARE COMMON IN THE YOUNGER-OLD.** Malek-Ahmadi M, Intorcchia AJ, Tremblay C, Arce RA, Walker J, Borja CI, Cline MP, Hemmingsen S, Stewart A, Qiji S, Martinez K, Krupp A, McHattie R, Sue LI, Serrano GE, Beach TG. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.
125. **CHARACTERIZATION OF ISOLATED HUMAN ASTROCYTES IN AGING AND LEWY BODY DISEASE.** Aslama S, Walker JE, Piras IS, Huentelman MS, Arce RA, Tremblay C, Glass MJ, Intorcchia AJ, Nelson CM, Suszczewicz KE, Borja CI, Cline MP, Hemmingsen SJ, Qiji SH, Mariner M, Krupp A, Martinez K, McHattie R, Stewart A, Beh ST, Beach TG, Serrano GE. Banner Sun Health Research Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.
126. **CLINICOPATHOLOGICAL CORRELATION: DOPAMINE AND AMYLOID PET IMAGING WITH NEUROPATHOLOGY IN THREE SUBJECTS CLINICALLY DIAGNOSED WITH ALZHEIMER'S DISEASE OR DEMENTIA WITH LEWY BODIES.** Gupta HV, Beach TG, Mehta SH, Shill HA, Driver-Dunckley E, Sabbagh MN, Belden CM, Liebsack C, Dugger BN, Serrano GE, Siderowf A, Pontecorvo MJ, Mintun MA, Joshi AD, Adler CH. The University of Kansas Health System; Banner Sun Health Research Institute; Mayo Clinic College of Medicine; Barrow Neurological Institute; Ruovo Clinic; University of California at Davis; University of Pennsylvania; Avid Radiopharmaceuticals; Arizona Alzheimer's Consortium.
127. **DYSREGULATION OF BRAIN INFLAMMATION IN COVID-19, AN AUTOPSY SERIES.** Serrano GE, Walker JE, Piras IS, Huentelman MS, Arce RA, Tremblay C, Glass MJ, Sue LI, Intorcchia AJ, Nelson CM, Suszczewicz KE, Borja CI, Cline MP, Hemmingsen SJ, Qijia SH, Aslam S, Mariner M, Krupp A, Martinez K, McHattie R, Stewart A, Beh ST, Beach TG. Banner Sun Health Research Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

128. **GENERATION AND CHARACTERIZATION OF SKIN-DERIVED PRECURSOR CELLS FROM HUMAN AUTOPSY-DERIVED SCALP FIBROBLASTS.** Beh ST, Mitchell L, Lue LF, Borja C, Arce R, Intorcio A, Walker J, Suszczewicz K, Cline M, Hemmingsen S, Qiji S, Krupp A, Martinez K, McHattie R, Stewart A, Mariner M, Tremblay C, Aslam S, Beach T, Serrano G. Banner Sun Health Research Institute; University of Maryland; Arizona Alzheimer's Consortium.
129. **INTERHEMISPHERIC ASYMMETRY IN THE PROGRESSION OF ALZHEIMER-TYPE TAUOPATHY.** Tremblay C, Serrano GE, Intorcio AJ, Walker JE, Arce RA, Curry J, Sue LI, Nelson CM, Glass MJ, Qiji SH, Borja CI, Cline MP, Suszczewicz KE, Hemmingsen SJ, Aslam S, Krupp A, Martinez K, McHattie R, Stewart A, Fleisher AS, Pontecorvo MJ, Atri A, Montine TJ, Chen K, Beach TG. Banner Sun Health Research Institute; Avid Radiopharmaceuticals; Eli Lilly and Company; Brigham and Women's Hospital and Harvard Medical School; Stanford University; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.
130. **LONG-TERM STORAGE EFFECTS ON P-TDP43 IMMUNOHISTOCHEMICAL AND HISTOCHEMICAL NEURODEGENERATIVE DIAGNOSTIC STAINING OF ARCHIVED PARAFFIN SECTIONS.** Intorcio AJ, Tremblay C, Arce RA, Walker J, Borja CI, Cline MP, Hemmingsen S, Stewart A, Qiji S, Martinez K, Krupp A, McHattie R, Sue LI, Beach TG, Serrano GE. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.
131. **NEUROPATHOLOGICAL DIAGNOSES OF SUBJECTS AUTOPSIED IN THE PHASE 3 CLINICOPATHOLOGICAL STUDY OF FLORTAUICIPR F18 PET IMAGING.** Beach TG, Montine TJ, Serrano GE, Sue LI, Intorcio AJ, Walker JE, Glass M, Tremblay C, Arce R, Suszczewicz K, Borja C, Cline M, Qiji S, Hemmingsen S, Stewart A, Martinez K, Krupp A, McHattie R, Beh ST, Aslam S, Mariner M, Fleisher AS, Pontecorvo MJ, Devous Sr. MD, Lu M, Mintun MA, on behalf of the A16 study investigators. Banner Sun Health Research Institute; Stanford University School of Medicine; Avid Radiopharmaceuticals; Arizona Alzheimer's Consortium.
132. **OLFACTORY BULB DEAFFERENTATION IN SUBJECTS DYING WITH COVID-19.** Tremblay C, Intorcio AJ, Walker JE, Arce RA, Borja CI, Suszczewicz KE, Cline MP, Hemmingsen SJ, Qiji SH, Sue LI, Nelson CM, Aslam S, Mariner M, Krupp A, Martinez K, McHattie R, Stewart A, Beh ST, Beach TG, Serrano GE. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.
133. **OLFACTORY BULB PATHOLOGY AND ITS INFLUENCE ON OLFACTORY FUNCTION IN AGING.** Tremblay C, Intorcio AJ, Walker JE, Arce RA, Qiji SH, Borja CI, Cline MP, Suszczewicz KE, Hemmingsen SJ, Aslam S, Mariner M, Krupp A, Martinez K, McHattie R, Stewart A, Beh ST, Sue LI, Wilson JR, Adler CH, Shill HA, Driver-Dunckley E, Mehta SH, Serrano GE, Beach TG. Banner Sun Health Research Institute; Arizona State University; Mayo Clinic Arizona; Barrow Neurological Institute; Arizona Alzheimer's Consortium.
134. **PATIENT-BASED POSTMORTEM FIBROBLAST BANKING FOR AGE-RELATED NEURODEGENERATIVE DISEASE RESEARCH.** Beh ST, Lue LF, Brafman DA, Frisch C, Churko J, Arce R, Borja C, Intorcio A, Walker J, Suszczewicz K, Cline M, Hemmingsen S, Qiji S, Krupp A, Martinez K, McHattie R, Stewart A, Mariner M, Tremblay C, Aslam S, Beach T, Serrano G. Banner Sun Health Research Institute; Arizona State University; University of Arizona; Arizona Alzheimer's Consortium.

135. **SEX DIFFERENCES IN ALZHEIMER'S DISEASE: MOLECULAR PATHWAY FOR SYNAPTIC LOSS.** Walker JE, Qiji S, Stewart A, Biddle B, Mesch K, Mitchell L, Tremblay C, Intorcio A, Arce R, Suszczewicz K, Borja C, Cline M, Hemmingsen S, Martinez K, Krupp A, McHattie R, Aslam S, Mariner M, Beh ST, Beach TG, Serrano GE. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.
136. **THE EFFECT OF AGING AND NEUROLOGICAL DISORDERS ON MUSCLE FIBER SIZE IN THE PSOAS MUSCLE: A PILOT STUDY.** Arce R, Beh ST, Intorcio A, Walker JE, Suszczewicz KE, Borja CI, Cline MP, Hemmingsen SJ, Qiji SH, Aslam S, Mariner M, Krupp A, Martinez K, McHattie R, Stewart A, Tremblay C, Beach TG, Serrano GE. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.



**Arizona Alzheimer's Consortium
23rd Annual Scientific Conference**

Oral Research Presentation

Abstracts

ORAL RESEARCH PRESENTATION

INITIAL FINDINGS FROM THE ALZHEIMER'S PREVENTION INITIATIVE AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE COLOMBIA TRIAL. Langbaum JB, Tariot PN, Lopera F, Rios-Romenets S, Hu N, Schiffman C, Clayton D, Bittner T, Giraldo-Chica M, Acosta-Baena N, Villegas G, Espinosa A, Londoño Castaño M, Muñoz C, Ospina P, Bocanegra Y, Tirado V, Henao E, Cardona E, Luna E, Lopez H, Sánchez G, Muñoz M, Jakimovich L, Su Y, Alexander R, Quiroz YT, Doody RS, Sink KM, Reiman EM, on behalf of the API ADAD Colombia Trial Group. Banner Alzheimer's Institute; Neurosciences Group of Antioquia, University of Antioquia; Genentech, Inc; F. Hoffmann-La Roche Ltd; Massachusetts General Hospital and Harvard University; Arizona Alzheimer's Consortium.

Background: Crenezumab is an anti-amyloid monoclonal antibody that binds to beta-amyloid (A β) oligomers and is hypothesized to prevent the buildup of pathogenic A β plaques and to modify Alzheimer's disease (AD) progression with a low risk of amyloid-related imaging abnormalities (ARIA). The Alzheimer's Prevention Initiative (API) Autosomal Dominant AD (ADAD) Colombia trial evaluated crenezumab using clinical and biomarker endpoints in cognitively unimpaired presenilin 1 (PSEN1) E280A mutation carriers recruited from the world's largest ADAD kindred (NCT01998841).

Methods: This randomized, double-blind, placebo-controlled, parallel-group phase 2b trial evaluated the efficacy, safety, and tolerability of crenezumab in cognitively unimpaired 30–60-year-old Colombian PSEN1 E280A kindred members whose median age of mild cognitive impairment onset is 44 years. The 252 trial participants included mutation carriers who were randomized to crenezumab, mutation carriers who were randomized to placebo, and non-carriers who received placebo distributed in an approximately 1:1:1 ratio; everyone was blinded to mutation status. While participant inclusion in the trial was independent of baseline amyloid positron emission tomography (PET) findings, 40% of the carriers were found to have a negative amyloid PET scan prior to treatment. While dosing started with 300 mg subcutaneously every 2 weeks, it evolved over time and participants were eventually treated with either crenezumab (up to 720 mg subcutaneously every 2 weeks or 60 mg/kg intravenously every 4 weeks) or placebo for 5–8 years using a common close design. The primary endpoint family included the change in the API ADAD Cognitive Composite Test score and the Free and Cued Selective Reminding Test score. Secondary clinical efficacy endpoints included time to clinical progression to MCI or dementia due to AD, time to Clinical Dementia Rating (CDR) score >0, and increase in CDR Sum of Boxes. Other clinical outcomes included FAST, NPI, MMSE, CERAD word recall and RBANS results. Most of the participants had serial amyloid PET, tau PET, 18F-FDG PET, magnetic resonance imaging, cerebrospinal fluid (CSF) and BBBM measurements and other assessments.

Results: Treatment with crenezumab was not associated with a significant clinical benefit in either of its co-primary endpoints assessing rate of change in cognitive abilities or episodic memory function, measured by the API ADAD Composite Cognitive Test Score and the Free and Cued Selective Reminding Test (FCSRT) Cueing Index, respectively. Numerical differences favoring crenezumab over placebo were observed across the co-primary and multiple secondary and exploratory endpoints but were not statistically significant.

Conclusion: The API ADAD Colombia Trial was intended to characterize the efficacy, safety, and tolerability of crenezumab in the prevention of AD; explore the treatment's differential biomarker effects in amyloid-positive and amyloid-negative participants at virtually certain AD risk; clarify relationships between the treatment effects on biomarker and clinical outcomes; provide a shared resource of data and samples for the field; help to establish a new era in AD prevention research; and advance the role of emerging BBBMs in these endeavors. Initial clinical, cognitive, and biomarker results will be presented along with a brief summary of the historical context and strategic aims of API and the API ADAD trial.

ORAL RESEARCH PRESENTATION

EFFECTS OF AEROBIC EXERCISE ON COGNITION AND IMAGING BIOMARKERS IN OLDER ADULTS WITH ALZHEIMER'S DISEASE DEMENTIA. Yu F, Salisbury D, Mathiason M, SeungYong H, Jack C. Arizona State University; University of Minnesota; Mayo Clinic Rochester; Arizona Alzheimer's Consortium.

Background: Aerobic exercise has shown no to moderate cognitive effects in older adults with Alzheimer's disease (AD) dementia. Mechanistically, aerobic exercise appears to favorably modify the accumulation, degradation, and removal of AD-hallmark amyloid- β and tau. However, human mechanistic studies are limited with mixed findings. Hence, the purpose of the FIT-AD Trial was to examine the effects of 6-month aerobic exercise on cognition and magnetic resonance imaging (MRI) biomarkers in community-dwelling older adults with AD dementia.

Methods: The FIT-AD Trial was a pilot RCT that first qualified participants for the main exercise study and then for MRI. Ninety-six participants were enrolled at the main exercise study level and randomized to moderate-intensity cycling or low-intensity stretching for 20-50 minutes, 3 times a week for six months on a 2:1 ratio with three age strata (66-75, 76-85, and 85+ years of age) and followed up for another six months. Sixty of the 96 participants met MRI eligibility with 59 enrolled (38 in cycling and 21 in stretching). Cognition was assessed at baseline, 3, 6, 9, and 12 months using the AD Assessment Scale-Cognition (ADAS-Cog). Discrete cognitive domains were measured using the AD Uniform Data Set battery. MRI biomarkers included hippocampal volume, temporal meta-regions of interest cortical thickness, white matter hyperintensity (WMH) volume, and network failure quotient (NFQ) and were measured at baseline, 6 months, and 12 months.

Results: On average, the 96 participants were 77.4 ± 6.8 years old with 15.6 ± 2.9 years of education, and 55% were male. The 6-month change in ADAS-Cog was 1.0 ± 4.6 for the cycling group and 0.1 ± 4.1 for the stretching group, which were both significantly less than the expected 3.2 ± 6.3 -point increase observed naturally with disease progression. The 12-month change was 2.4 ± 5.2 (cycling) and 2.2 ± 5.7 (control). ADAS-Cog did not differ between groups at 6 ($p=0.386$) and 12 months ($p=0.856$). There were no differences in the 12-month rate of change in ADAS-Cog (0.192 vs. 0.197 , $p=0.967$), memory (-0.012 vs. -0.019 , $p=0.373$), executive function (-0.020 vs. -0.012 , $p=0.383$), attention (-0.035 vs. -0.033 , $p=0.908$), or language (-0.028 vs. -0.026 , $p=0.756$). The MRI subsample ($n=59$) were similar to the overall sample at 77.3 ± 6.3 years old with 15.6 ± 2.9 years of education and 53% men. Both the cycling and stretching groups experienced significant declines in hippocampal volume (2.64% vs. 2.89%) and cortical thickness (0.94% vs. 1.54%) over 6 months and over 12 months (hippocampal volume: 4.47% vs. 3.84%; cortical thickness: 2.27% vs. 1.79%). These declines didn't differ between groups. WMH volume increased significantly, but the cycling group increased >50% less than the stretching group (10.9% vs. 24.5% over 6 months [$f=4.47$, $p=.04$]; 12.1% vs. 27.6% over 12 months [$f=5.88$, $p=.02$]). NFQ didn't change significantly over time nor differed between groups.

Conclusions: Aerobic exercises may reduce cognitive decline but its effect is likely small and dose-dependent. The cognitive effects of aerobic exercise may be explained by its impact on hippocampal volume and cortical thickness. While aerobic exercise is effective on reducing WMH progression, which may not translate to improved cognition or functional connectivity.

ORAL RESEARCH PRESENTATION

CLINICAL PREDICTORS OF ALZHEIMER'S DISEASE DEVELOPMENT IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT USING SYNTHETIC DATA DERIVED FROM VETERANS AFFAIRS ELECTRONIC HEALTH RECORDS. Irwin CM, Tjandra D, Aggarwal V, Hu C, Giordani B, Wiens J, Migrino RQ. Phoenix VA Healthcare System; The University of Arizona College of Medicine – Phoenix; University of Michigan; MD Clone; Arizona Alzheimer's Consortium.

Background: Current methods of predictive modeling for Alzheimer's disease (AD) rely heavily on AD-specific biomarkers that are either difficult or costly to obtain. Use of electronic health record (EHR) data leverages extensive multidimensional data from routine care encounters that could be used to identify clinical conditions that predict AD conversion from mild cognitive impairment (MCI). Synthetic data derived from the original patient data very closely resemble the original data but are truly non-identifiable because individual data does not relate to any real individual. Our goal is to identify clinical predictors of MCI to AD conversion using synthetic data that closely resemble VA EHR data.

Methods: Synthetic data produced by MD Clone software derived from Veterans Affairs (VA) Corporate Data Warehouse (CDW) EHR data were used to construct our study's cohort. From a dataset of 1,998,650 unique patients, we included patients with an MCI diagnosis between the ages of 62 and 67 and at least 10 years of follow-up or conversion to AD within 10 years in our final cohort (N = 11,262). ICD-9/10 codes were used to categorize patient comorbidities either present or absent at time of MCI diagnosis. Demographics and commonly associated AD comorbid conditions for AD were used in the model. A multivariate Cox proportional hazard model with forward stepwise selection was used to develop a final model of independently predictive variables.

Results: In the 41,376 patients diagnosed with MCI the median age of MCI onset was 64.73 years (IQR: 63.04 – 66.68). Our final study cohort was predominantly white (77.1%) and male (97.0%). A total of 2,424 out of 11,262 (21.5%) patients converted from MCI to AD within 10 years. The median conversion time was 4.26 years (IQR: 2.03 – 6.55). Renal failure (HR: 1.83, 95% CI: 1.38 – 2.42), cerebral infarction (1.33, 1.17 – 1.52), liver disease (1.33, 1.16 – 1.52), sleep apnea (1.26, 1.15 – 1.38), type II diabetes (1.21, 1.11 – 1.32), depression (1.17, 1.07 – 1.27), hyperlipidemia (1.11, 1.01 – 1.23), age (1.26, 1.22 – 1.29), and BMI (0.95, 0.95 – 0.96) were independently predictive of AD conversion within 10 years. Heart failure, coronary heart disease, atrial fibrillation, atherosclerosis, myocardial infarction, hypertension, hypothyroidism, hyperthyroidism, osteoporosis, glaucoma, rheumatoid arthritis, history of smoking, and alcohol abuse were removed by forward stepwise selection from the final model.

Conclusions: Patient EHRs provide valuable information that can be leveraged to develop AD prediction models that may have clinical utility in identifying patients at high risk of AD. Use of synthetic data extend the ability to analyze non-identifiable data for model building but may encode incorrect assumptions. Our immediate next task is to validate the performance of the model using synthetic data with real patient data and to develop a predictive nomogram that can be used to estimate an individual patient's risk for AD conversion from MCI.

ORAL RESEARCH PRESENTATION

STATIN RESPONDER ANALYSIS FOR PRECISION PREVENTION OF ALZHEIMER'S DISEASE. Torrandell-Haro G, Branigan GL, Rodgers KE, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.

Background: Previously we identified reduced risk of Alzheimer's Disease (AD) in statin users (Torrandell-Haro et al. 2020). Identifying the subgroup of responders is an important step towards a precision statin therapy approach. This study aimed to investigate the effect of statin therapy on the incidence of Alzheimer's Disease (AD) and other age-related neurodegenerative diseases (NDD) by therapy, sex, and age group. Moreover, it sought to identify and describe responder vs non-responder phenotypes to statin therapy based on demographic characteristics, comorbidity burden, and drug exposure.

Methods: A retrospective analysis was conducted using a US-based insurance claims dataset of 53 million participants. Inclusion criteria included participants aged 45 years old or older, with no prior history of NDD before statin use, and with claims enrolled for at least 6 months prior and 3 years after start of statin therapy. A propensity score-matched based on age, gender, region, comorbidities and cci was applied for group assignment. Records were surveyed for a diagnosis of AD 1 year after statin exposure. Sensitivity analyses for the detection of responders based on comorbidities and drug combinations were conducted.

Results: Of the 1,293,952 participants who met inclusion criteria, 646,976 participants were exposed to statin therapy and were propensity score-matched to 646,976 patients without exposure. Statin use was associated with a decreased risk of AD (RR [95% CI]: 0.50 [0.48–0.52]; $P < .001$) and other NDD. Additionally, men exhibited a greater risk reduction than women for non-AD dementia. Responders had a higher incidence of obesity and asthma whereas non-responders were predominantly female and had an overall higher incidence of cardiovascular and cerebrovascular comorbidities.

Conclusions: Statin use was associated with a reduced risk of AD and other NDD, replicating previous results. Non-responders were predominantly women with a high incidence of cardiovascular comorbidities. Characterization of responders to statin exposure advances a precision prevention approach, in which prescription guidelines consider neurological health and are adapted for at-risk populations.

ORAL RESEARCH PRESENTATION

HEPARIN TREATMENT IS ASSOCIATED WITH A DELAYED DIAGNOSIS OF ALZHEIMER'S DEMENTIA IN ELECTRONIC HEALTH RECORDS FROM TWO LARGE UNITED STATES HEALTH SYSTEMS. Readhead B, Klang E, Gisladdottir U, Vandromme M, Li L, Quiroz YT, Arboleda-Velasquez JF, Dudley JT, Tatonetti NP, Glicksberg BS, Reiman EM. Arizona State University; Banner Alzheimer's Institute; Icahn School of Medicine at Mount Sinai; Tel Aviv University; Columbia University; Massachusetts General Hospital and Harvard Medical School; Schepens Eye Research Institute of Massachusetts Eye and Ear; Sema4; University of Arizona; Arizona Alzheimer's Consortium.

Background: Recent studies suggest that heparan sulfate proteoglycans (HSPG) contribute to the predisposition to, protection from, and potential treatment and prevention of Alzheimer's disease (AD). Here, we used electronic health records (EHR) from two different health systems to examine whether heparin therapy was associated with a delayed diagnosis of AD dementia.

Methods: Longitudinal EHR data from 15,183 patients from the Mount Sinai Health System (MSHS) and 4,990 patients from Columbia University Medical Center (CUMC) were used in separate survival analyses to compare those who did or did not receive heparin therapy, had a least 5 years of follow-up data, were at least 65 years old by their last visit, and had subsequent diagnostic code or drug treatment evidence of possible AD dementia. Analyses controlled for age, sex and comorbidities.

Results: Heparin therapy was associated with significant delays in age of clinical diagnosis of AD dementia, including +1.0 years in the MSMS cohort ($P < 0.001$) and +1.0 years in the CUMC cohort ($P < 0.001$).

Conclusions: While additional studies are needed, this study supports the potential roles of heparin-like drugs and HSPGs in the protection from and prevention of AD dementia.

ORAL RESEARCH PRESENTATION

CEREBRAL MICROVASCULAR DYSFUNCTION IN 5X-FAD MICE: ROLE OF BIOLOGICAL SEX, BK CHANNEL ACTIVITY AND OXIDATIVE STRESS. Silva JF, Savu A, Polk FD, Kath AM, Pires PW. University of Arizona College of Medicine, Tucson; Arizona Alzheimer's Consortium.

Background: Vasculopathy is present in patients with Alzheimer's disease (AD) and it may contribute to disease progression and severity, via poorly understood mechanisms. Markers of oxidative stress are present in the brain of AD patients, as well as in transgenic mouse models. This increase in reactive oxygen species can lead to oxidative damage in macromolecules, including proteins, which can alter their function. Large conductance calcium activated K⁺ channels (BKCa) are one of such targets in vascular smooth muscle cells; these channels play an important role in vasodilatory responses and maintenance of myogenic tone in resistance arteries. Opening of BKCa channels occurs upstream from localized intracellular Ca²⁺ release events (Ca²⁺ sparks), and results in K⁺ efflux, vascular smooth muscle cell hyperpolarization and vasorelaxation. In a pro-oxidative scenario, BKCa can be oxidized, resulting in decrease activity and exacerbation of contractile responses, which can compromise cerebral blood flow regulation, generating an environment that may accelerate neurodegeneration. We hypothesized that reduction in BKCa-dependent vasodilation in cerebral arteries, as consequence of oxidative stress, results in neurovascular dysfunction in the 5x-FAD model of AD.

Methods: Posterior communicating arteries (PComA) from 5 months-old male and female 5x-FAD and wild-type (WT) littermates were isolated and studied in ex vivo using pressure myography. Calcium (Ca²⁺) sparks in smooth muscle cells were evaluated by spinning-disk confocal microscopy. Oxidative stress levels were assessed by total and oxidized glutathione levels in the brain using a colorimetric enzymatic assay. Basal cortical perfusion and functional hyperemia were evaluated by laser speckle contrast imaging. Data are means ± SEM, analyzed by two-tailed Student's t-test.

Results: In females, PComA from 5x-FAD showed higher spontaneous myogenic tone than WT (Myogenic tone: 24.48 ± 3.20 vs $16.09 \pm 0.93\%$, 5x-FAD vs WT, $p < 0.05$, $N = 7$). Constriction to iberiotoxin (30 nM, BKCa blocker) was smaller in 5x-FAD than WT, suggesting lower basal BKCa activity (Vasoconstriction: -4.252 ± 0.429 vs $-9.220 \pm 2.556\%$, 5x-FAD vs WT; $p < 0.05$; $N=5$), which was independent of alterations in intracellular Ca²⁺ sparks activity (Frequency: 0.51 ± 0.30 vs. 0.62 ± 0.33 Hz, 5x-FAD vs WT, $p > 0.05$, $N=3-4$). No differences in constriction induced by 60 mM KCl or endothelin-1 (30 nM) were observed in PComA from 5x-FAD when compared to WT. These vascular changes were associated to higher levels of oxidative stress in whole brain homogenates of 5x-FAD ([oxidized glutathione]: 7.83 ± 0.62 vs 5.27 ± 0.74 μM, 5x-FAD vs WT, $p < 0.05$, $N=8$), lower resting cortical perfusion atop the frontal cortex (Perfusion: 345.9 ± 16.43 vs. 415.5 ± 23.15 PU, 5x-FAD vs WT, $p < 0.05$, $N = 6$), and impaired functional hyperemia responses after whisker stimulation (increase from baseline: 3.82 ± 0.64 vs. $9.91 \pm 1.41\%$, 5x-FAD vs WT, $p < 0.05$, $N = 6$). No significant differences were observed between male 5x-FAD and WT for all parameters studied.

Conclusions: Cerebrovascular impairments were more pronounced in female 5x-FAD mice, observed as an increase in spontaneous myogenic tone, likely due to reduction in smooth muscle cell BKCa activity associated to an increase in brain oxidative stress. These alterations were linked to reduced basal cortical perfusion and blunted neurovascular coupling responses.

ORAL RESEARCH PRESENTATION

DEEP LEARNING APPLICATION IN RETINAL IMAGING CLASSIFICATION OF ALZHEIMER'S DISEASE. Dumitrascu OM, Zhu W, Qiu P, Nandakumar K, Wang Y. Mayo Clinic Arizona; Arizona State University; Washington University; Arizona Alzheimer's Consortium.

Background: Alzheimer's Disease (AD) has increasing prevalence with vast societal and public health implications. There is a critical unmet need to develop biomarkers for early AD diagnosis. Recent scientific advances underscore retinal vascular changes and retinal abnormal protein deposition mirroring the changes in the AD brain. We have previously shown that retinal vascular tortuosity correlate with neurocognitive dysfunction and may predict AD. Retinal fundus photography is a cost-effective and high-resolution imaging tool to study retinal vascular changes in AD and emerge as a noninvasive biomarker for early AD diagnosis and monitoring. Handcrafted identification of the retinal vascular features on color fundus images is laborious, subjective, and prone to bias. Hence, developing automated retinal imaging tools has attracted strong research interest. Here, we leverage deep neural networks to develop an automatic framework to classify AD and extract AD retinal fundus imaging biomarkers using weakly supervised localization and Gradient-weighted Class Activation Mapping.

Methods: Our proposed framework is a two-stage system informed by previous research supporting retinal vascular dysfunction in AD. We used non-mydratic color retinal fundus images from AD patients from Mayo Clinic and cognitively normal controls (NC) from the Eyepacs database. In the first stage, a U-Net based network was applied to raw macula-centered and optic-disc-centered fundus images to produce vascular segmentation. The obtained binary vessel segmentation was subsequently fed into the encoder of the U-Net for feature extraction. The feature extractor is initialized with the weights from the first stage since the contextual features from the U-Net encoder is useful for classification. The extracted features were fed to an average pooling layer and a fully connected layer with a Softmax activation to output probabilistic prediction.

Results: The U-Net is pretrained on the Digital Retinal Images for Vessel Extraction (DRIVE) dataset. We selected one image with the best segmentation from each subject, which resulted in 40 training images and 16 testing images. The problem is formulated as a binary classification task with positive class (AD) and negative class (NC). Our trained model achieved an area under ROC curve (AUC-ROC) of 0.938 on the testing set. The generated 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 optic head are highlighted in NC. Overall, our proposed network identifies retinal blood vessel branches with tortuosity change as potential identifier of AD.

Conclusions: We present a novel retinal imaging-based deep learning analysis framework for AD screening. Our preliminary results in a small data set demonstrated the feasibility of our DL model and a strong promise to identify automated retinal imaging biomarkers for AD diagnosis. Future research will include larger datasets of AD and preclinical AD subjects.

ORAL RESEARCH PRESENTATION

LONGITUDINAL MOTOR DECLINE IN DEMENTIA WITH LEWY BODIES AND PARKINSON DISEASE DEMENTIA IN THE ARIZONA STUDY OF AGING AND NEURODEGENERATIVE DISEASE. Choudhury P, Zhang N, Adler CH, Chen K, Belden C, Driver-Dunckley E, Mehta SH, Shprecher DR, Serrano G, Shill HA, Beach TG, Atri A. Banner Sun Health Research Institute; Mayo Clinic Arizona; Barrow Neurological Institute; Brigham and Women's Hospital; Harvard Medical School; Arizona Alzheimer's Consortium.

Background: Parkinson's Disease Dementia (PDD) shares several clinical and pathological features[1] and is the second most common misdiagnosis for Dementia with Lewy Bodies (DLB) after Alzheimer's Disease (AD)[2]. Parkinsonism is a core feature of both PDD and DLB[3] but the diagnosis is dependent on the timing of emergence of motor symptoms relative to cognitive symptoms. Limited information is available about the characteristics and evolution of parkinsonian motor features in PDD and DLB an arbitrary 1-year cut off[4]. We examined the progression of extrapyramidal symptoms and signs in autopsy-confirmed Dementia with Lewy bodies (DLB), Parkinson's Disease Dementia (PDD) and Alzheimer's Disease (AD).

Methods: Over 1435 participant years of longitudinal data were derived from the AZSAND with PDD (n=98), AD (n=48) and DLB (n=48) further sub-grouped as with or without parkinsonism (DLB+ and DLB-). Within-group UPDRS-II and UPDRS-III trajectories, and subscales were analyzed using non-linear mixed effects model.

Results: Parkinsonism was present in 65.6% of DLB cases. Baseline UPDRS-II and III scores were highest ($p < 0.001$) for PDD (mean \pm SD 14.3 \pm 7.8 and 27.4 \pm 16.3), followed by DLB+ (6.0 \pm 8.8 and 17.2 \pm 17.1), DLB- (1.1 \pm 1.3 and 3.3 \pm 5.5) and AD (3.2 \pm 6.1 and 8.0 \pm 13.5). Compared to PDD, the DLB+ group had faster UPDRS-III progression over 8 years (Cohen's-d range 0.98 to 2.79, $p < 0.001$) driven by gait ($p < 0.001$) and limb bradykinesia ($p = 0.02$) subscales.

Conclusions: DLB+ progresses faster than PDD providing insights about change in motor function.

ORAL RESEARCH PRESENTATION

ADVANCING EVIDENCE-BASED ADRD CAREGIVER INTERVENTIONS THROUGH TECHNOLOGY. Gómez-Morales A, Coon DW. Arizona State University; Arizona Alzheimer's Consortium.

Background: Between 2020 and 2025, the projected increase in people living with Alzheimer's disease (AD) in Arizona will be 33.3%, the largest percentage in the nation. This increase is accompanied by a simultaneous need for family caregivers to assist loved ones with advancing AD. Family caregiving can be very challenging and stressful taking a toll on caregiver health, emotional well-being, and other quality of life indicators. Evidence-based psychoeducational and skill-building interventions, such as Care Partners Reaching Out (CarePRO), have proven to be effective in reducing caregiver stressors and related distress. Caregiver participants who are employed, live in rural areas, and/or face transportation barriers and their service providers have asked for alternatives to in-person intervention delivery. The COVID-19 pandemic accelerated this need to adapt CarePRO for video-conferencing (Zoom-based) delivery. As new technologies have become more affordable, VR has begun to be incorporated into evidence-based caregiver interventions to enhance the experience of embodying a person with Alzheimer's, resulting in innovations in caregiver intervention approaches.

Methods: This presentation focuses on the integration of technology into two evidence-based psycho-educational skill-building interventions via single-arm feasibility and acceptability pilot studies. (1) The adaptation of CarePRO for Zoom-based delivery (CarePRO Virtual); this intervention was conducted over five weeks, lasting 2.5 hours per session in groups of approximately 5 to 8 Latina caregivers with accompanying coach calls for skills reinforcement. (2) Through Alzheimer's Eyes (TEA) combines psychoeducation, skill-building and Virtual Reality that allows caregivers to experience what it is like to have AD. Both interventions include opportunities to learn about the disease, apply skills such as relaxation, management of challenging behavior, and communication.

Results: Twenty-five self-identified Latinas completed CarePRO Virtual and twenty caregivers of different races/ethnicities completed TEA. In terms of feasibility and acceptability, delivery for both interventions has been successful with high intervention retention rates and minimal technological challenges, reaching caregivers both within and outside of Arizona. Technological challenges were few and isolated to participants with limited experience with technology. Caregivers reported strong overall benefits from the interventions and expressed interest in joining similar projects offered by our team in the future.

Conclusions: CarePRO Virtual and Through Alzheimer's Eyes are innovative interventions that leverage existing technology to help address the evolving needs of caregivers. Results suggest that psycho-educational skill-building interventions can incorporate VR learning activities and can be delivered via video conferencing platforms successfully. Feedback from the participants provided rich data to guide future intervention development merging advances in technology to reach diverse communities of caregivers.

ORAL RESEARCH PRESENTATION

NEUROGENETICS OF AGING VOICE AND IMPLICATIONS FOR NEURODEGENERATIVE DISEASES. Vishwanath SH, McCarthy FM, Peter B, Gordon M, Story B, Samlan R, Miller JE. University of Arizona; Arizona State University; Arizona Alzheimer's Consortium.

Background: At least thirty percent of adults will experience deficits in vocal production that emerge at middle age and become more prevalent after age 65 affecting quality of life. Vocal disorders can arise due to natural aging processes as well as neurodegenerative diseases. Treatment options target the larynx with behavioral therapy or surgical approaches. To expand treatment options and support early disease intervention, we need to identify the affected brain mechanisms. To do so, we utilize the adult male zebra finch songbird because they have dedicated vocal control regions in the brain that are anatomically and genetically similar to humans. We discovered that middle-aged finches have noisier, louder, and faster songs compared to young adults and consistent with the breathy, hoarse, disordered voice detected in aged humans. We hypothesize that abnormal gene expression patterns in the finch basal ganglia contribute to these age-related vocal changes.

Methods: To test our hypothesis, tissue biopsies were obtained from Area X, a song-dedicated basal ganglia nucleus in the adult male finch, following two hours of solo singing or quiet across young, middle, and old adult groups (n=12 birds/group). Total RNA was isolated and sequenced, and reads mapped to the zebra finch genome followed by generation of differentially expressed mRNA transcripts. Birdsongs from the singing groups were segmented into individual syllables in Praat, and acoustic features extracted as in our prior study (Badwal et al. Behav Neurosci, 2020).

Results: A comparison of young adult versus middle age singers or to old singers yielded 130 and 211 differentially expressed mRNA transcripts, respectively ($p < 0.05$). Cell motility, migration, neurogenesis, and plasma membrane pathways were highly enriched in these datasets. A comparison of middle age to old adult singers yielded 177 differentially expressed genes with the most enrichment in ribosomal and cellular component pathways. When comparing datasets by age only, irrespective of behavioral state (singing versus quiet), nuclear, metabolic, and MAPK signaling processes were the top pathways. A comparison of singing versus quiet behavioral states, irrespective of the bird's age, revealed MAPK signaling, ribosomal and protein processing as the most enriched pathways. Across ages in singing birds, we identified 41 genes from our dataset whose mRNA expression is also altered in human Parkinson's Disease, including those that code for transcription factors, transmembrane, and cytoskeletal proteins. Two genes (MRPL17, NCK2) that code for mitochondrial ribosomal and adaptor proteins are also linked to Alzheimer's Disease. We found eight genes that are linked to speech and language disorders, including a gene that codes for a GABAergic receptor (GABRD) and another for a voltage-gated calcium channel (CACNA2D1). Twenty-eight genes are also associated with autism susceptibility. Genetic data will be correlated to our acoustic results to hone in on critical molecular pathways in finch Area X for further investigations.

Conclusions: Our finch model offers a robust data set for quantifying relationships between vocal measures, age, and genetic changes in the brain. The transition between young, middle and old ages offers critical time points for identifying vocally-associated molecular pathways and cellular mechanisms that are most vulnerable to diseases of aging. Targeting these mechanisms with drug and gene-based approaches offers an opportunity for early intervention and treatment.

ORAL RESEARCH PRESENTATION

FLORBETAPIR PET MEASUREMENTS OF AMYLOID PLAQUE DEPOSITION ARE MORE CLOSELY CORRELATED WITH CROSS-SECTIONAL AND LONGITUDINAL COGNITIVE AND CLINICAL MEASUREMENTS USING A WHITE MATTER REFERENCE REGION OF INTEREST. Bhargava V*, Wang M*, Chen Y, Luo J, Weiner M, Landau S, Jagust W, Su Y, Reiman EM, Chen K, (*first coauthors). University of Arizona College of Medicine Phoenix; Banner Alzheimer's Institute; Arizona State University; Translational Genomics Research Institute; University of California San Francisco; University of California Berkeley; Arizona Alzheimer's Consortium.

Background: Quantification of the relationship between brain metabolism and amyloid deposition has been limited by variance in A β deposition measurements. We previously reported stronger statistical associations of FDG-PET measured glucose hypometabolism with A β deposition quantified using Standard Uptake Value Ratio (SUVR) with a cerebral white matter reference region-of-interest (SUVRwmRef) compared to the commonly used SUVR with cerebellar reference region-of-interest (SUVRcrblm) both cross-sectionally and longitudinally (Wang et al., AAIC 2021). The goal of this study was to compare cross-sectional and longitudinal associations of SUVRwmRef and SUVRcrblm with various cognitive/clinical measures.

Methods: Our study population consisted of 1133 participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) including 206 participants clinically diagnosed with AD dementia, 563 with Mild Cognitive Impairment (MCI), and 364 cognitively unimpaired individuals (CU). We computed partial correlation of SUVRwmRef or SUVRcrblm, covarying out baseline age and years of education, with: Mini Mental State Exam (MMSE); Sum Boxes, Clinical Dementia Rating Scale (CDR-SB); Alzheimer's Disease Assessment Scale (ADAS11, ADAS13); Auditory Verbal Learning Test – Short Term Memory, Long Term Memory, and Total (AVLT STM, AVLT LTM, and AVLT Total respectively). Steiger's Z-test was used to determine the SUVRwmRef and SUVRcrblm correlation coefficient differences with each of these cognitive/clinical measures at uncorrected $p=0.05$ significance. These analyses were carried out over all subjects and within each diagnostic group, first for baseline data and then longitudinally for changes of these measures.

Results: Cross sectionally, correlations were significantly stronger with SUVRwmRef than with SUVRcrblm for all subjects in all eight cognitive/clinical measures (Steiger's test, all $p<7.6e-07$) with the strongest correlation of SUVRwmRef with ADAS13 (Pearson Correlation: $r=0.40$ for SUVRcrblm and $r=0.53$ for SUVRwmRef; Steiger's Test: $p=1.64e-19$). Within CU and MCI individuals, the strongest correlation of SUVRwmRef with ADAS13 was also observed (CU: $r=0.06$ for SUVRcrblm and $r=0.16$ for SUVRwmRef; Steiger's test $p=0.0013$; MCI: $r=0.29$ for SUVRcrblm and $r=0.34$ for SUVRwmRef; Steiger's test $p=0.0032$). The strongest correlation within AD subjects was found between SUVRwmRef and ADAS11 ($r=0.11$ for SUVRcrblm and $r=0.22$ for SUVRwmRef; Steiger's Test $p=0.0016$). Within AD individuals, correlations between AVLT STM and amyloid burden was not significant ($p=0.13$). Longitudinally, similar stronger SUVRwmRef correlations than SUVRcrblm with each of these cognitive measures were also observed.

Conclusions: Cerebral white matter reference regions for florbetapir PET demonstrate stronger and statistically significant associations between amyloid deposition and cognitive measures than results using cerebellar reference region. We conclude cerebral white matter reference region is superior to cerebellar reference region for amyloid PET analysis.

ORAL RESEARCH PRESENTATION

HEAD-TO-HEAD COMPARISON OF FOUR PLASMA PHOSPHO-TAU IMMUNOASSAYS IN THE NEUROPATHOLOGICAL DIAGNOSIS OF ALZHEIMER'S DISEASE. Malek-Ahmadi M, Ashton NJ, Karikari TK, Beach TG, Serrano GE, Chen Y, Chen K, Ghisays V, Hansson O, Palmqvist S, Janelidze S, Su Y, Zetterberg H, Dage J, Blennow K, Reiman EM. Banner Alzheimer's Institute; University of Gothenburg; University of Pittsburgh; King's College London; NIHR Biomedical Research Centre for Mental Health, South London & Maudsley NHS Foundation; Banner Sun Health Research Institute; Lund University; Skåne University Hospital; Indiana University School of Medicine; Arizona State University; University of Arizona; Arizona Alzheimer's Consortium.

Background: Plasma ptau is a promising indicator of amyloid- β ($A\beta$) mediated tau pathophysiology. We previously characterized the ability of Lilly's MesoScale Discovery (MSD)-based plasma ptau217 and ptau181 assays to discriminate between those with and without the neuropathological diagnosis of Alzheimer's disease (AD) in Banner research participants with near-end-of-life blood samples and extensive postmortem neuropathological assessments. We now extend this work in a head-to-head comparison of those assays to the University of Gothenburg's Single molecule array (Simoa)-based plasma ptau181 and 231 assays.

Methods: Assays were performed blindly in plasma samples acquired 1.0 ± 0.7 years before death from up to 106 Banner research participants with and without cognitive impairment and different neuropathological diagnoses. ROC analyses were used to discriminate between those with and without the neuropathological diagnosis of AD and presence or absence of neuritic $A\beta$ plaques. Spearman correlations were used to characterize their associations with mean cortical neuritic plaque counts and with mean cortical tau tangle counts in those with and without the diagnosis of AD or neuritic plaques.

Results: Lilly's ptau217 assay was better than Lilly's ptau181 and Gothenburg's ptau231 and ptau181 assays in discriminating between the neuropathological diagnosis of Intermediate/High Likelihood versus Low Likelihood/No AD (respective AUCs=0.86, 0.67, 0.62 and 0.61), the diagnosis of High Likelihood versus Low Likelihood/No AD (AUCs=0.95, 0.83, 0.67 and 0.67), and presence or absence of neuritic $A\beta$ plaques (AUCs=0.86, 0.70, 0.61 and 0.62). It also provided better indicators of mean cortical neuritic plaque (r 's=0.69, 0.35, 0.26 and 0.29) and tangle counts (r 's=0.73, 0.60, 0.19, -0.04) in those with the neuropathological diagnosis of AD or at least moderately frequent neuritic plaques (r 's=0.71, 0.59, 0.22, 0.01). The assays were not correlated with tangle counts in those without AD or neuritic plaques.

Conclusions: Lilly's MSD-based plasma ptau217 assay performed better than the other three ptau assays in the neuropathological diagnosis of AD, discriminating between those with and without neuritic $A\beta$ plaques, and providing an indicator of $A\beta$ -related tau tangle burden. Banner's growing brain donation program resources could help characterize and compare blood-based biomarkers in the neuropathological diagnosis of AD, Parkinson's disease and related diseases.



**Arizona Alzheimer's Consortium
23rd Annual Scientific Conference**

Student Poster Presentation

Abstracts

ADULTHOOD CHOLINE SUPPLEMENTATION IN THE TS65DN MOUSE MODEL OF DOWN SYNDROME. Tallino SL, Bartholomew SK, Sepulveda I, Winstone JK, Velazquez R. Arizona State University; Arizona Alzheimer's Consortium.

Background: Choline metabolism lies at the heart of multiple cognition-relevant pathways, with choline sourced both from the diet and from endogenous metabolic pathways. Adequate choline is particularly important for cognition in Down syndrome (DS) in humans and in Ts65Dn mice, the most commonly used DS rodent model. Past work has shown that maternal choline supplementation improves hippocampal-dependent cognitive outcomes for Ts65Dn offspring, an effect which persists during aging even after supplementation has ceased. This is particularly relevant given the established link between DS and Alzheimer's disease (AD), with the majority of DS patients developing AD pathology by 40 years of age and dementia by 70. However, whether adult initiation of choline supplementation in the Ts65Dn can improve AD-relevant outcomes has yet to be determined in the Ts65Dn mouse model.

Methods: Here, we placed trisomic (3N) and disomic (2N) Ts65Dn mice (n = 16-18 per diet per genotype, balanced by sex; Jackson Laboratory Strain #005252) on diets containing either 1.1 mg/kg (ChN) or 5 mg/kg (Ch+) choline chloride from 4.5 months until endpoint at 14 months old, a total of 38 weeks of diet regimens. Blood was collected at baseline and at endpoint, and enzyme-linked immunosorbent assay (ELISA) and glucose tolerance was measured at endpoint. Animals were also assessed behaviorally by rotarod (for motor function) and radial arm water maze (RAWM; for spatial memory) at 12.5 mo.

Results: By 32 weeks, we observed a highly significant main effect of sex on percent weight change, with females gaining markedly more weight than males overall, and a modest main effect of diet, with animals on Ch+ diets gaining less weight; these changes were independent of food intake, which was not significantly different between groups. Analysis of serum using ELISA showed a significant decrease in serum choline as a function of age, suggesting Ch+ diets did not prevent age-related decline in circulating choline. Glucose tolerance measured at endpoint revealed a significant effect of Ch+ diet lowering fasting glucose, but no changes to recovery from glucose challenge. Behavioral analysis revealed no significant difference in locomotion. RAWM data revealed a significant effect of genotype on latency to platform and correct/total arm entry ratio, but no effects of choline diet.

Conclusions: Adulthood choline supplementation does not appear to ameliorate hippocampal-dependent cognitive deficits observed in trisomic mice, emphasizing the importance of prenatal and early-life dietary intervention. However, supplementation did ameliorate age-associated weight gain in female mice and improved fasting blood glucose, suggesting modest impact of a Ch+ diet on risk factors associated with AD.

AGE-RELATED ALTERATIONS IN REPRESENTATIONAL FORMS OF IMAGINATION: A NOVEL SCORING PROTOCOL APPLIED TO AUTOBIOGRAPHICAL MEMORY.
Hovhannisyan M, Chau N, Deffner A, Andrews-Hanna JR, Grilli MD. University of Arizona; Arizona Alzheimer's Consortium.

Background: Human imagination is a complex system that allows us to form images or concepts in the mind that are not present to the senses. Research on imagination has been heavily influenced by the idea that humans store two distinct types of long-term memory: episodic and semantic memory. This theoretical distinction is particularly important in the context of aging, where older adults show reduced episodic memory compared to semantic memory. However, recent work has shown that these two memories are not as distinct as once thought (Renoult, 2019; Irish, 2020).

Methods: Here, we propose to use a framework outlined by Andrews-Hanna and Grilli (2021), which suggests that memory and future thinking are the outcome of the collaboration between two representational forms of imaginative thought: the mind's mind and the mind's eye. The mind's mind is described as a verbal or auditory form of imagination and the mind's eye is described as an image-based form of imagination. In this study, we apply a novel scoring protocol based on these two forms of imaginative thought to autobiographical memory data, to capture the interactions between episodic and semantic memory in older age. Eighty-two cognitively normal older adults retrieved unique autobiographical events, and were instructed to focus on describing the episodic, or event-specific, details.

Results: All data were scored according to the new scoring protocol and the autobiographical interview guidelines from Levine et al., 2002. Our novel scoring protocol demonstrated high inter-rater reliability across two raters for both mind's mind (0.95) and mind's eye (0.96) details. First, we show that proportion of mind's mind and mind's eye details on average are not significantly different. Second, consistent with prior research, we find that older age is significantly associated with reduced episodic detail generation. Lastly, we find that mind's eye detail production is reduced with age while mind's mind detail production remains steady.

Conclusions: Our scoring protocol shows a different capturing of episodic and semantic memories, indicating an overlap between the two and implications for studying memory in older adults.

AGING-ASSOCIATED MEDIN INDUCES HUMAN BRAIN MICROVASCULAR ENDOTHELIAL CELL PRO-INFLAMMATORY AND PRO-THROMBOTIC ACTIVATION VIA NFkB. Nabaty NL, Karamanova N, Truran S, Morrow K, Schafer R, Li M, Migrino RQ. University of Arizona College of Medicine-Phoenix; Phoenix VA; Arizona Alzheimer's Consortium.

Background: Vascular aging involves acquiring a phenotype characterized by proinflammatory and prothrombotic milieu, endothelial dysfunction, and calcification. It is responsible for aging-associated pathologies such as cardio-cerebro-vascular disease, vascular dementia (VaD), Alzheimer's disease (AD), and related dementias. The underlying mechanisms behind vascular aging remain poorly understood. Medin, a 50 amino acid cleavage product of milk fat globule EGF factor 8, accumulates in the vasculature with aging and is associated with VaD and AD. We showed that medin causes endothelial dysfunction and endothelial cell proinflammatory activation, making it a prime candidate as molecular mediator of vascular aging. Our goal is to test the hypotheses that medin induces proinflammatory and prothrombotic changes in human brain microvascular endothelial cells (HBMVECs) and that these changes are mediated by nuclear factor kappa B (NFkB).

Methods: HBMVECs were exposed to either vehicle, recombinant medin (5 μ M, a physiologically relevant dose observed in human tissues) without or with RO106-9920 (a small molecule selective NFkB inhibitor, 10 μ M), or RO106-9920 alone for 20 hours. Cell lysates were measured for gene expression of inflammatory cytokines/chemokines/adhesion molecules (IL-6, IL-8, IL-1b, ICAM-1 and VCAM-1) and thrombotic factors (thrombomodulin (TM), a transmembrane glycoprotein that is a potent inhibitor of coagulation, plasminogen activator inhibitor-1 (PAI-1) which promotes thrombosis and tissue factor (TF) which initiates the coagulation cascade) using real time quantitative polymerase chain reaction.

Results: HBMVECs treated with medin showed increased IL-6 ($3.1\pm 0.6x$ versus vehicle), IL-8 ($3.8\pm 0.5x$), IL-1b ($14.2\pm 9.1x$), ICAM-1 ($5.4\pm 1.2x$) and VCAM-1 ($35.5\pm 12.9x$), all $p < 0.05$, signifying increased pro-inflammatory activation. HBMVECs treated with medin showed reduced TM ($0.6\pm 0.1x$ versus vehicle) and increased PAI-1 ($2.5\pm 0.3x$), both $p < 0.05$, signifying increased prothrombotic activation, although TF gene expression was not changed ($0.95\pm 0.1x$, $p = NS$). Co-treatment of medin with RO106-9920 prevented the increases in IL-6 ($1.2\pm 0.3x$), IL-8 ($2.0\pm 0.1x$), IL-1b ($1.2\pm 0.3x$), ICAM-1 ($1.6\pm 0.1x$), VCAM-1 ($0.4\pm 0.2x$), and the reduction in TM ($0.9\pm 0.1x$). However, co-treatment with RO106-9920 did not alter medin's effect on PAI-1 ($2.4\pm 0.8x$).

Conclusions: Medin caused increased pro-inflammatory gene expression in HBMVECs. It also caused reduced TM and increased PAI-1 gene expression, but no change in TF in HBMVECs. Co-treatment with NFkB inhibitor prevented medin's proinflammatory effect and effect on TM but not PAI-1. The findings demonstrate the role of medin in endothelial cell activation that may contribute to vascular aging phenotype and as a potential novel therapeutic target.

AGING WITH TRAUMATIC BRAIN INJURY: EVALUATION OF NEUROPATHOLOGY, AXONAL INJURY, NEUROINFLAMMATION, AUTOPHAGY, AND PTAU PATHOLOGY IN THE DENTATE GYRUS AT 6-MONTHS POST-INJURY. Rajaboina B, Krishna G, Mian E, Sabetta Z, Bromberg C, Baun J, Zurhellen C, Adelson PD, Currier Thomas T. University of Arizona College of Medicine-Phoenix; Barrow Neurological Institute at Phoenix Children's Hospital; Arizona State University; Neuroscience Associates; Phoenix VA Health Care System; Arizona Alzheimer's Consortium.

Background: Traumatic brain injury (TBI)-induced Wallerian degeneration and secondary injury sequelae are associated with persisting neuroinflammation hypothesized to increase risk or early-onset of neurodegenerative diseases.

Methods: At 6-months post-midline fluid percussion injury (FPI), we evaluated markers of neuropathology (amino cupric-silver stain), axonal injury (APP), neuroinflammation (Iba-1; GFAP), autophagy (neutral red), and phospho-tau (AT8) pathology in the dentate gyrus (DG) of the hippocampus in male and female Sprague Dawley rats (n=5-6/group).

Results: Positive silver stain was present in injured and age-matched shams; however, the organization, localization, and amount of neuropathology were region-dependent within the DG. After FPI, punctate pathology was predominantly found within the inner granule layer vs. sham, where punctate and neuronal pathology was predominant in the granule cell layer. Positive APP pathology was present in sham and injured white matter tracts. Microglia number, branch length/microglia, and endpoints/microglia were similar between groups, although visual assessment revealed non-uniform presentation of activated morphologies indicative of a neuroinflammatory response. Evaluation of a time course of glial activation at 7-, 56-, and 168DPI indicated a time \times injury interaction ($F(2,51)=17.47$; $p<0.0001$) where activation follows an independent and different time course in sham ($p<0.05$) vs. injured ($p<0.05$) DG. A 45% increase in neutral red staining was present in FPI compared to sham ($p<0.05$). No AT8 staining was observed in the DG or other brain regions. No quantifiable sex differences were detected.

Conclusions: Different distribution of neuropathology, glial activation time courses, and evidence of persistently activated autophagy pathways implicate novel differences between age- and aging-with-injury-related neuropathological processes requiring further investigation.

Funding-NIH_R01NS100793_Phoenix_Children's_Hospital_Mission_Support.

ANALYSIS OF MICROSTRUCTURAL FEATURES OF BONNET MACAQUE LOCUS COERULEUS- CENTRAL TEGMENTAL TRACT USING MRI MICROSCOPY. McDermott K, Laurel Dieckhaus L, Gray DT, Hutchinson EB, Barnes CA. University of Arizona; University of California, Los Angeles; Arizona Alzheimer's Consortium.

Background: The locus coeruleus (LC) is a brainstem nucleus with many targets throughout the cortex. Projections to the cortex from the LC 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 thoroughly defined. Analysis of LC-cortical tractography has historically been difficult due to the small size of the LC and the abundance 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 CTT with respect to age.

Methods: We performed high resolution ex-vivo MRI on perfused whole brains of 3 adult (10-11 years) and 3 aged (21-25 years) female bonnet macaques. Scans included diffusion tensor imaging (DTI) scans using 3D echo planar imaging with high (1500-3000,4500) b-value shells at 600µm resolution, multi-spin echo (MSE) T2 scans at 600µm resolution, and T1 FLASH and selection inversion recovery (SIR) scans at 200µm resolution. T1 FLASH images were used for manual segmentation of regions of interest (ROIs). MRtrix was used for constrained spherical deconvolution to generate fiber orientation density (FODs) and probabilistic tracts from the LC to the thalamus (CTT). Generated tracts were used to calculate tract length and number and converted into ROI masks to extract Fractional Anisotropy (FA), Myelin Water Fraction (MWF), and Bound Pool Fraction (BPF) of the CTT. These MRI metrics from diffusion and relaxometry based techniques offer insight into brain microstructures to quantify myelin and microstructural integrity. Preliminary ROI analysis revealed no difference between the aged and adult group in terms of size of the tract, or FA, BPF, and MWF values.

Results: In conclusion, our anatomy based tractography methods allowed us to successfully generate LC tracts anatomically consistent with the CTT. The older cohort of animals did not differ from the younger animals in the size or integrity of the white matter of the LC-CTT tract.

Conclusions: If these results hold and the integrity of this tract is preserved in old age, this could be a promising biomarker for differentiating healthy aging from pathological aging. Future directions include transforming the tracts into template space for analysis and analyzing the behavioral performance of these animals relative to microstructure.

APOE ϵ 4-ALLELE IS ASSOCIATED WITH REDUCED HIPPOCAMPAL VOLUME IN OLDER ADULTS WITH AUTISM SPECTRUM DISORDER. Al-Hassan L, Lewis, C, Braden BB. Arizona State University; Arizona Alzheimer's Consortium.

Background: It has been shown that middle-aged and older adults (MA+) with autism spectrum disorder (ASD) have a higher chance of developing Alzheimer's disease (Alz) when compared to neurotypical (NT) adults (Vivanti et al., 2021). We and others demonstrated that individuals with ASD are more likely to carry the apolipoprotein E (APOE) ϵ 4 allele (Giunco et al., 2009), the strongest genetic risk factor for Alz. Our study aims to determine if carrying APOE ϵ 4 allele negatively impacts memory function and hippocampal volume in MA+ ASD compared to NT adults.

Methods: Participants were 62 intellectually able middle-aged and older adults over the age of 40, including 30 with ASD [mean age=54 (\pm 8.7)] and 32 NT adults [mean age=52.5 (\pm 7.8)]. APOE allelic distribution was determined from salivary samples via polymerase chain reaction amplification and genotyped on a tapestation. Baseline hippocampal volumes were derived using FreeSurfer and corrected for total intracranial volume. The Auditory Verbal Learning Test measured short- and long-term verbal memory. The immediate recall of the first trial measured short-term memory, while the twenty-minute delayed trial measured long-term memory.

Results: MA+ ASD APOE ϵ 4 carriers had smaller left hippocampal volumes compared to MA+ ASD APOE ϵ 4 non-carriers ($p=0.033$). The right hippocampus approached significance ($p=0.056$). In addition, the interaction between ASD diagnosis and ϵ 4 allele status approached significance for the left ($p=0.092$) and right ($p=0.10$) hippocampus. APOE ϵ 4 carriers in both MA+ ASD and NT groups had reduced short-term memory performance compared to non-carriers ($p=0.049$). However, the ϵ 4 allele status did not affect long-term memory.

Conclusions: This study suggests MA+ ASD APOE ϵ 4 carriers are at greater risk for reduced hippocampal volume than MA+ ASD APOE ϵ 4 non-carriers. Carrying APOE ϵ 4 allele indicates an increased risk of developing Alz. Future research is needed to replicate our findings using a larger sample and further understand how the ϵ 4 allele affects memory and hippocampal volume in MA+ ASD.

BINDING AND DISRUPTION OF AMYLOID BETA AND TAU PLAQUES VIA FOCUSED ULTRASOUND AND TARGETED PHASE SHIFT MICROBUBBLES IN A MOUSE MODEL OF ALZHEIMER'S DISEASE. Murphy D, Howison C, Lusk J, Unger E, Meuillet E, Trouard T. University of Arizona; Microvascular Therapeutics; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is the most prevalent neurodegenerative disease in the United States, and accounts for 60% to 70% of dementia cases. AD has been associated with the accumulation and aggregation of Amyloid Beta (AB) aggregates and Tau neurofibrillary tangles, which is linked to the progression of AD. One of the greatest obstacles in treatment of neurodegenerative disease is the blood-brain barrier (BBB), which prevents most therapeutic agents from entering the brain. Microvascular Therapeutics (MVT) has developed a novel microbubble (MB) ultrasound contrast agent (MVT-100), that when used in conjunction with focused ultrasound (FUS) can temporarily and reversibly disrupt the BBB. Using a proprietary process, MVT has also been able to condense MVT-100 into Phase Shifted Microbubbles (PSMBs). These PSMBs were engineered to bind and disrupt AB and Tau protein aggregates once the BBB has been transiently opened.

Methods: MVT-100 microbubbles and PSMBs are formulated in-house at MVT. The majority (>80%) of microbubbles are 0.5-1.0 um in diameter, with larger diameter MB present in smaller amounts. The formulation is similar to Definity microbubbles, with several proprietary changes that increase the stability and reduce the known adverse effects of back pain. The targeted PSMBs are approximately 150-250 nm in diameter and are formulated using a similar method as the MB, but with additional patent-pending procedures to formulate the bioconjugates within the PSMBs. For some experiments, PSMBs were formulated with a DiD fluorescent dye. Preliminary experiments were conducted in C57/Blk6 control mice to validate the use of the MB, FUS, and PSMBs in-vivo. The experimental protocol included an IP injection of Gadolinium DTPA (which allows for BBB opening visualization in the MRI), followed by IV injection of MVT-100 MB. Immediately following MB injection, the focused ultrasound transducer was placed on the mouse's scalp and turned on for 30 seconds at 0.01 kW/cm². Following sonication, mice underwent T1-weighted MRI to confirm BBB opening. After BBB opening was confirmed, mice were given an IV injection of PSMBs, which was allowed to circulate for 15 minutes. The mouse was then perfused, and the brain was excised, sectioned and imaged with fluorescence microscopy to determine PSMBs presence in the brain tissue.

Results: Results indicate that the BBB can reversibly be disrupted in WT mice using a combination of MVT-100 MB and FUS at a low power setting. The experiments also demonstrated that the MB and FUS is well-tolerated, with minimal tissue damage in the area of sonication. Fluorescence microscopy indicated that fluorescently labeled PSMBs are present in the brain after BBB opening, and that they are only present in the tissue immediately surrounding the region of BBB opening.

Conclusions: Preliminary results demonstrate that the FUS with MB can transiently disrupt and open the BBB and allow the targeted PSMBs to enter the brain. Future work will involve transgenic AD mouse models, and the binding of PSMBs and disruption of AB and Tau plaques will be quantified using fluorescence microscopy, IHC staining and blood analyses.

CELLULAR MODELS FOR THE INVESTIGATION OF STRUCTURAL DYNAMICS AND ACTIVITY OF HUMAN TAU PROTEIN AGGREGATE FORMATION. Ranaweera E, Huseby CJ, Hansen DT, Chiu PL, Serrano GE, Beach TG, Fromme P. Arizona State University; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium

Background: Mounting evidence for the central role of tau protein in Alzheimer's disease (AD) highlights the need for deep investigation of intracellular tau aggregation pathways and formation of aberrant tau polymorphs within cellular models. Intrinsically disordered proteins with low sequence complexity like hyperphosphorylated tau protein can form condensed folded structures that contribute to neurodegeneration. Candidates for aberrant intracellular tau folding and aggregation have been identified including liquid-liquid phase separation (LLPS) and we will investigate if nanocrystal growth at ribosomes could be observed. Recent research discovered that the differences in tau folding at the core of pathological tau aggregates can differentiate AD from other tauopathies. It is hypothesized that disease specific changes in the cellular environment surrounding tau, such as patterns of hyperphosphorylation, could lead to differential core structures. This exciting new structural information showing tau aggregates are unique to each tauopathy opens the door to a structural approach for elucidating mechanisms of pathogenic tau aggregation pathways in cellular model systems and AD brain.

Methods: Combining advanced structural determination methods including cryoEM, cryoFIB, and cryo-electron tomography, we are working on direct imaging of intracellular tau aggregates in cells as well as autopsy tissue derived from human brain. The goal is to develop exciting new cellular models of human tau aggregation using both mammalian and insect cell lines which we employ to systematically test intracellular forces necessary to create unique pathological tau structures beginning with patterns of hyperphosphorylation.

Results: We successfully overexpressed the six human tau isoforms in both Sf9 insect cells and SH-SY5Y mammalian cells and induced this intracellular tau to form aggregates by incubating the cells with a small molecule tau aggregation inducer Congo Red. Additionally, using cryo-focused ion beam, we are able to mill thin lamellae through vitrified cells which we will use for future cryo-tomography imaging and 3D reconstruction.

Conclusions: The development of our cellular models of tau aggregation will allow us to manipulate intracellular environments resulting in the generation of tau aggregates. Using advanced structural methods, we can compare our aggregates with authentic human brain-derived AD tau aggregates as well as visualize intracellular interactions.

COGNITIVE EFFECTS OF UNOPPOSED ESTROGENIC HORMONE THERAPY IN TWO RODENT MODELS OF SURGICAL MENOPAUSE. Asadifar S, Bernaud VE, Wu ES, Bandin EA, Peña VL, Pastor JA, Highton LE, Andrew KB, Bimonte-Nelson HA. Arizona State University; Arizona Alzheimer's Consortium.

Background: The onset of menopause results in a variety of symptoms, including vasomotor, mood, and cognitive alterations. Women can be prescribed hormone therapy (HT) to help alleviate such symptoms. Hysterectomy, the surgical removal of the uterus, is the second most common gynecological surgery in women. Clinically, hysterectomy has been shown to increase the risk of dementia in women, and we have recently shown unique cognitive outcomes in the rat, with hysterectomy alone impairing cognition. Women without a uterus can take unopposed HT; that is, containing only estrogens. The neurocognitive effects of unopposed HT after hysterectomy have not been systematically studied.

Methods: The current study utilized the rat model to evaluate the effects of 17-beta-estradiol (E2) HT after two common variants of surgical menopause: hysterectomy or ovariectomy (Ovx, surgical removal of the ovaries). Rats received either Sham surgery (n=10), Ovx (n= 20), or Hysterectomy (n=20), followed by administration of Vehicle (polyethylene glycol; n=10 per group) or E2 (n=10 per group for Ovx and Hysterectomy). Behavioral testing was then performed to investigate spatial working and reference memory, and multiple physiological markers of hormonal and overall health status were obtained.

Results: Preliminary analyses demonstrated that Ovx significantly impaired performance, hysterectomy marginally impaired performance, and E2 obviated these deficits. It is notable that different surgical menopause types impacted different portions of the learning curve.

Conclusions: Our poster will present detailed behavioral and physiological analyses, focusing upon the effects of unopposed HT after hysterectomy versus Ovx for different cognitive domains, as well as broader physiological effects.

DATA MINING THE NATIONAL ALZHEIMER'S COORDINATING CENTER (NACC) UNIFORM DATA SET TO DETERMINE ASSOCIATIONS BETWEEN MRI AND DEMENTIA. Schatz S, Comrie C, Dieckhaus L, Hutchinson E. University of Arizona; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is generally accompanied by brain atrophy, which can be evident on MRI based evaluation at late stages of the disease, but there is a need for earlier stage MRI markers that may predict later atrophy and progressive cognitive impairment. In a post-mortem MRI study of human hippocampal tissue, we have observed an increase in both mean diffusivity and T2 with greater Braak stage providing a foundation for this secondary retrospective analysis utilizing the National Alzheimer's Coordinating Center (NACC) Uniform Data Set. Focusing on the changes in multiple MRI metrics as they correlate with cognitive impairment, a pipeline was developed for computing normalized and quantitative maps of combined metrics for use in whole brain, ROI (region of interest), and voxel-wise analysis.

Methods: From an initial 7,276 distinct subjects with MRI data acquired from the NACC repository dataset, 1,005 subjects were selected based on the presence of a DTI (Diffusion Tensor Image), T2-weighted MRI, and global Clinical Dementia Rating Scale (CDR). A single site (6499) of 464 subjects was selected due to consistent image formatting, and while CDRs of 0, 0.5, 1, 2, and 3 are present, the two extremes, CDR of 0 (no dementia, n=37) and 3 (severe cognitive impairment, n=278), were selected for initial analysis to develop a robust pipeline for computing combined maps. DTI data was processed through a TORTOISE pipeline to correct motion and EPI distortion using a structural image as a target. Tensor maps were then computed to achieve the desired Trace map. BET2 was used to extract the brain from the skull and in the creation of masks. To generate semi-quantitative T2 maps from T2-weighted MRI scans, all T2 images were normalized to their respective cerebral spinal fluid (CSF) under the assumption that CSF signal intensity is uniform across subjects. Due to the atrophy present in the majority of subjects, Atropos segmentation was performed with three tissue types to ensure only regions of CSF were selected for normalization. The trace map for each brain was then divided by its corresponding normalized T2, thus computing a map with combined metrics for each subject.

Results: Scans acquired for each subject from the NACC data subset have been processed resulting in a combined map in addition to the individual DTI metrics. An initial whole brain analysis indicates a significant difference in distribution of the average whole brain intensities between CDR of 0 and 3 in trace (Mann–Whitney U = 694, p = 0.000), normalized T2 (Mann–Whitney U = 3950, p = 0.022), and trace divided by normalized T2 (Mann–Whitney U = 2130, p = 0.000) maps. The normalized T2 (d = 0.397) has a medium Cohen's effect size, while trace (d = 2.436) and trace divided by normalized T2 (d = 1.017) have large effect sizes.

Conclusions: The DTIs for all 315 subjects are currently being registered to the Human Connectome Project (HCP) 1065 DTI template using DRTAMAS (Diffeomorphic Registration for Tensor Accurate Alignment of Anatomical Structures). With all the brains in a common space, voxel-wise analysis will be performed to identify abnormal voxels as well as ROI based analysis to specifically consider the hippocampal region, for comparison with the post mortem study findings.

DECONSTRUCTING THE BLOOD BRAIN BARRIER: EVALUATION OF CORTICAL ASTROCYTIC CHANGES SURROUNDING MICROVASCULATURE POST-TBI. Sabetta Z, Krishna G, Willayard FA, Curry T, Adelson PD, Thomas TC. University of Arizona; Barrow Neurological Institute at Phoenix Children's Hospital; Phoenix VA Healthcare System; Arizona State University; Northwestern University; Arizona Alzheimer's Consortium.

Background: Diffuse traumatic brain injury (TBI)-induced astrogliosis is implicated in long-term post-TBI recovery and morbidity, with where blood-brain barrier (BBB) permeability is specifically implicated in increased risk for neurodegenerative diseases. Post-TBI astrogliosis influences neuroprotection, neurorepair, neuropathology and BBB permeability; however, few studies have evaluated the temporal pathology as a function of aging-with-injury and sex-dependence, including morphological evaluation around cerebrovasculature.

Methods: Male and female late-adolescent Sprague Dawley rats (n=5-6/group; total=64) were subjected to sham surgery or midline fluid percussion injury (FPI). At 7-, 56-, and 168-days post-injury (DPI), brains were processed for immunohistochemical analyses to evaluate GFAP+ staining intensity in cortex without large vessels and a skeleton analysis and neuronal tracing of astrocyte branch projections around cortical penetrating arterioles using 40x and 100x brightfield microscopy, respectively.

Results: Cortical GFAP intensity changes as a function of FPI ($p > 0.0001$), DPI ($p < 0.0001$), and FPI×DPI ($p < 0.0001$); where FPI-induced astrogliosis was greatest at 7DPI and declined over time ($p < 0.001$) and age-related astrogliosis increased overtime ($p < 0.05$). Sex×FPI approached significance ($p = 0.07$), with interactions occurring at 168DPI. An interim analysis indicates astrocyte branching increased near penetrating arterioles at 7DPI compared to shams ($p < 0.05$), appearing to form additional end feet that were no longer present at 168DPI.

Conclusions: These data show different temporal profiles of astrogliosis as a function of aging and aging-with-injury, where distinct morphological changes around cerebrovasculature at acute time points are indicative of injury-induced functional or structural mechanisms mediating post-TBI cerebrovascular homeostasis, warranting further investigation as to whether changes are protective or pathological.

DESIGNING A METHOD OF PRIME INDUCED NUCLEOTIDE ENGINEERING USING A TRANSIENT REPORTER FOR EDITING ENRICHMENT (PINE-TREE). Kostes W, Frisch C, Galyon B, Whitman B, Brafman D. Arizona State University; Arizona Alzheimer's Consortium.

Background: Prime editing is a versatile gene editing method that mediates targeted insertions and deletions, and can perform all 12 types of point mutations without the induction of deleterious double-strand breaks. We designed a method using a fluorescent reporter of prime editing titled prime induced nucleotide engineering using a transient reporter for editing enrichment (PINE-TREE). PINE-TREE is a fluorescent reporter-based enrichment strategy to rapidly generate clonal isogenic cell lines using prime editing. Here, we demonstrate a significant increase in editing efficiency when using PINE-TREE across multiple cell types and genomic loci. Most notably, we reveal PINE-TREE as a method to accelerate the generation of clonal human induced pluripotent stem cells (hiPSCs) harboring mutations in the APOE locus, a risk factor associated with altered probability of the onset of sporadic Alzheimer's Disease. Evidence from this investigation demonstrates PINE-TREE as a valuable resource for enhancing prime editing and expediting the generation of clonal isogenic cell lines for disease modeling.

Methods: Conventional cell enrichment strategies utilize a reporter of transfection (RoT) however, these methods fail to distinguish between edited and unedited cells during genome modification. To overcome this limitation, the Brafman laboratory developed a fluorescent-based assay for the real-time identification of edited cells. This method employs a BFP variant that upon targeted cytidine-base editing converts to a GFP. Using fluorescent activated cell sorting (FACS), we can efficiently isolate bulk populations or clones that have the desired genomic edit. Following lipofection of plasmids, edited cells are sorted via FACS and downstream Sanger sequencing used to quantify editing efficiency. This method will be used to compare PINE-TREE editing efficiency to conventional RoT enrichment strategies across multiple genomic loci and multiple cell types.

Results: This method was tested in hiPSCs. PINE-TREE displayed significantly higher editing efficiency compared to RoT to perform a substitution mutation, reaching editing efficiencies as high as 85%. We then compared single nucleotide mutation clonal editing efficiency of PINE-TREE and RoT in hiPSCs. Comparatively, TREE-enriched clones displayed a greater number of clones with the desired edit than RoT-enriched clones. Next, we compared the efficiency of PINE-TREE and RoT to perform single and triple nucleotide insertions and deletions at the HEK3 locus. PINE-TREE demonstrated a significant increase in editing efficiency compared to RoT when performing insertions and deletions, showing editing efficiencies as high as 65%. Lastly, we tested the ability of PINE-TREE to rapidly generate clonal isogenic hiPSCs harboring mutations in the APOE locus. We observed PINE-TREE to increase the yield of clones that harbor the desired edit compared to a conventional RoT enrichment method.

Conclusions: Here we described a method for enrichment of prime edited-cells that used a fluorescent reporter for editing enrichment known as PINE-TREE. PINE-TREE exhibited a significant increase in the ability to perform substitution, insertion, and deletion mutations in hiPSCs compared to a RoT enrichment strategy. Lastly, PINE-TREE exhibited greater clonal editing efficiencies across multiple genomic sites including the disease-relevant APOE locus. Together, this data suggests PINE-TREE as a method to enhance prime editing and accelerate the generation of clonal isogenic hiPSC lines for disease modeling.

DEVELOPMENT OF NONLIPOGENIC ABCA1 INDUCERS AS ALZHEIMER'S DISEASE THERAPEUTICS. Laham M, Lewandowski C, LaDu MJ, Reddy VG, Ackerman-Berrier M, Rychetsky P, Penton C, Reddy MS, Thatcher G. University of Arizona; University of Illinois at Chicago; Arizona Alzheimer's Consortium.

Background: The apolipoprotein E (apoE) E4 allele, the strongest known risk factor for sporadic Alzheimer's disease (AD), detrimentally impacts multiple aspects of AD pathology, including cholesterol homeostasis, inflammation, insulin resistance, and amyloid pathology. The pathogenesis of AD and related dementia (ADRD) has shown to be a multifaceted system with no singular target. Most drugs in development have been focused on amyloid- β which has not been fruitful. Liver X receptors (LXRs) have been proposed as drug targets due to their control over cholesterol transport genes (apoE, ABCA1), enhancement of insulin signaling, and repression of inflammatory markers. However, LXRs also mediate transcription of SREBP1c, the master regulator of liver triglyceride synthesis. The goal of this project is the development of nonlipogenic ABCA1 inducers (NLAI) to enhance lipidation of apoE, improve brain cholesterol transport, inflammation, and insulin resistance, without adverse lipogenic effects.

Methods: Several hits were previously identified that increased ABCA1 expression with minimal effects on inducing SREBP1c. The most promising hit was optimized via chemical synthesis to enhance its efficacy and potency toward ABCA1 induction. Improved probes were further tested in primary glia cultured from human apoE-expressing mice to explore their effects on lipid transport, inflammation, and insulin resistance. Additionally, two probes were tested for effects on insulin resistance, inflammation, and amyloid pathology in both high-fat diet and EFAD mouse models.

Results: Multiple novel probes with improved activity were successfully developed, the best of which demonstrated sub-micromolar potency toward ABCA1 induction in vitro. Selective induction of ABCA1 (vs. SREBP1c) expression, improved cholesterol transport, and diminished inflammatory responses were observed in primary mouse glia, HepG2, and J774 cell cultures. In mice placed on a high-fat diet, NLAI treatment reduced insulin resistance without elevating triglycerides or causing liver steatosis. Positive readouts were observed in EFAD mice.

Conclusions: Our studies represent a proof-of-concept for development of novel small molecules as NLAI. Although NLAI development without LXR activity is a possibility, the incorporation of LXR β -mediated activity has advantages demonstrated by previous work on LXR agonist; however, this depends on attenuating or eliminating lipogenic effects. Additional work is ongoing to improve NLAI potency, identify targets in addition to LXR, and improve oral and brain bioavailability.

DUAL AMELIORATION OF NEUROFIBRILLARY TANGLES AND AMYLOID PLAQUES WITH DYR219: A POTENT AND SELECTIVE SMALL MOLECULE FOR DYRK1A. Fistrovich A, Foley C, Velazquez R, Ow A, Oddo S, Meechoovet B, Dunckley T, Shaw A, Smith B, Hulme C. University of Arizona; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Dual-specificity tyrosine phosphorylation-regulate kinase 1A (DYRK1A) is found in postmortem human brains, and when overexpressed is linked to pathway breakdowns that contribute to Alzheimer's disease (AD)^{1,4}. Herein, we discuss DYR219, a small molecule that has demonstrated its potency and selectivity against DYRK1A⁶⁻⁷. Through in vivo based studies reduction of Tau, amyloids, and the promotion of DYRK1A degradation was observed in 3xTg-AD mice models⁷. Results suggest that therapeutic strategies involving kinase inhibition early in pathway breakdown and the overall progression of AD could prove promising.

Methods: Methods used in this work include synthesis, structure-based drug design, KD and IC50 determinations, KinomeScan, microsomal stability (time independent and time independent), solubility studies, in vivo pharmacology (3xTgAD model), in vivo behavioral studies, in vitro phosphorylation assay, western blot, ELISA, and pharmacokinetic studies of DYR219 in mouse.

Results: Here we report that DYR219 delays the onset of AD-like pathologies through DYRK1A inhibition in 3xTg-AD mice. At 6 months of age, the 3xTg-AD mice have no neurofibrillary tau (NFT) pathology and minimal amyloid plaque pathology in the CA1 region of the hippocampus. After 3 months of treatment with DYR219, the treated 3xTg-AD mice were cleared of both amyloid and tau neuropathology's, compared to the vehicle treated mice. Here we clearly demonstrate that, if DYRK1A inhibitors are administered prior to NFT formation, the onset of subsequent NFT pathology can be significantly delayed. This suggests that therapies targeting tau hyperphosphorylation will likely show the greatest effect if administered very early in the disease process. Furthermore, it is demonstrated that chronic DYRK1A inhibition reduces insoluble forms of amyloid beta peptides (A β) and hyper-phosphorylated tau long-term and that these reductions are associated with dramatic delay in the onset of both amyloid plaques and NFTs. Additionally, it was discovered that DYR219, devoid of a proteolysis targeting chimera, induces Dyrk1a degradation, contributing to the efficacy of this small molecule approach in vivo. Collectively, these results suggest that therapeutic strategies targeting tau phosphorylation will show the greatest effect if administered very early in the pathogenesis of AD.

Conclusions: The poster describes the development of a potent and selective small molecule, DYR219. The full profile of DYR219 is presented showing insight to its pharmacokinetic and pharmacodynamic ability. Although there are metabolic and oral bioavailability issues that need to be addressed, DYR219 has established itself as a potent DYRK1A inhibitor based on its inhibition of pS396 and total tau in in vitro phosphorylation assays. In vivo studies in 3xTg-AD revealed a delay in NFT and amyloid plaques development when treated with DYR219. Reduction of pS396, total tau, and amyloid plaques were also confirmed in these models. Further, through a western blot it was unearthed that DYR219 promotes DYRK1A degradation via proteasome.

EFFECT OF ADUCANUMAB-MEDIATED AMYLOID CLEARANCE ON DISEASE-ASSOCIATED MICROGLIA. Cadiz MP, Haug KA, Fryer JD. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Aducanumab is a therapeutic anti-amyloid antibody that is FDA-approved to treat mild Alzheimer's disease (AD). Although aducanumab mediates substantial amyloid clearance, its effects on microglia, the resident immune cells of the brain that are implicated in AD, are unknown. During AD, and in response to amyloid, microglia assume an activated "disease-associated microglia" (DAM) phenotype marked by transcriptional changes and associated with neuroinflammation. It is unclear whether DAM activation is reversible following amyloid clearance, and if so, whether this contributes to the progression of AD. The inflammatory role of DAM in AD suggests amyloid clearance alone may be insufficient to ameliorate microglia-mediated disease effects. Furthermore, the effect of cessation of aducanumab treatment, and subsequent re-accumulation of amyloid, on microgliosis and neuroinflammation is also unknown.

Methods: To determine how aducanumab treatment modifies microglial phenotypes, we administered aducanumab or IgG control via intraperitoneal injection to 10.5-month-old APP/PS1 mice, a model of amyloidosis. We harvested mice at the following timepoints: (1) one week after two weekly injections, and (2) one week after four weekly injections, to assess the acute effect of aducanumab, and (3) fifteen weeks after four weekly injections, to assess the effect of withdrawal of treatment. Microglial activation and phenotypes were assessed in each cohort by flow cytometry, RT-qPCR, and immunofluorescence.

Results: After two weekly doses of aducanumab, DAM-related genes including Trem2 were upregulated, accompanied by an increase in the proportion of Cd11c+ activated microglia as measured through flow cytometry. These Cd11c+ microglia were highly compacted, clustering densely around plaques. This suggests that aducanumab treatment increases microglial activation acutely. Interestingly, fifteen weeks after cessation of treatment, microglial activation was reduced in aducanumab-treated mice, which decreased both the expression of DAM genes and the number of Cd11c+ microglia compared to IgG controls.

Conclusions: These data demonstrate that aducanumab increases microglial activation early in treatment, suggesting an initial wave of microgliosis is part of the mechanism of aducanumab-mediated plaque clearance. However, following plaque clearance and withdrawal of treatment, microglial activation is decreased. This may be due to the decreased amyloid load in the brain, implying a reduction of a DAM-activating signal may allow these activated microglia to revert to a more homeostatic phenotype.

EFFECT OF APOE ALLELIC ISOFORM AND AGE ON CAROTID ARTERY FUNCTION AND VASCULAR REACTIVITY. Souders LJ, Hoxha B, Vallejo-Elias J, Jones C, Virden T, Jones TB, Eckman DM. Midwestern University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is the most common form of dementia and is one of the leading causes of death in the US. Growing evidence supports a link between AD and cardiovascular disease (CVD). Interestingly, variant isoforms of apolipoprotein E (APOE) are risk factors for both AD and CVD. The most common APOE isoform, APOE3, has a neutral risk for developing AD, whereas APOE4 increases the risk for AD. We hypothesized that APOE allelotype would affect carotid artery function and vascular reactivity. Carotid arteries (CAs) were isolated from mice expressing human-APOE targeted replacement of APOE3 (B6.129P2-Apoetm2(APOE*3)Mae N8) and APOE4 (B6.129P2-Apoetm3(APOE*4)Mae N8; Taconic Labs). We determined CA vascular function by assessing passive mechanical characteristics and vascular reactivity in the left main CA isolated from young (Y, 3-4mos), adult (Ad, 11-13mos) and aged (Ag, 18-22mos), homozygous APOE3 and APOE4, male and female mice.

Methods: CAs were rapidly isolated from age-matched male and female, APOE3 and APOE4 mice, cleaned of connective tissue, cut into 8mm segments, and cannulated in an arteriograph chamber to assess vascular reactivity to phenylephrine (PE)- and 60mM [K+]-induced constriction. In addition, passive wall tension, arterial wall thickness, vascular distensibility, and arterial stress/strain were measured at intraluminal pressures ranging from 10mm Hg to 140mm Hg.

Results: Our data using CAs from homozygous APOE3 and APOE4 male and female mice suggests nominal allelic distinctions for all age matched cohorts (Y, Ad, and Ag) when challenged with potassium chloride. Allelic effects on PE-induced constriction were most pronounced in Y mice ($P < 0.05$). Additionally, stress vs strain values displayed statistical significance for Y and Ag mice ($P < 0.0001$). Distensibility ($P = 0.002$), wall thickness ($P = 0.008$), and passive wall tension ($P = 0.034$) were significantly altered in Ag mice.

Conclusions: We previously reported age-related changes in isolated CAs from homozygous APOE3 and APOE4 male and female mice. Our current data supports that in otherwise healthy animals, aged mice that are homozygous for the APOE4 allele display greater carotid artery stiffening than aged, homozygous APOE3 mice. Future studies have been designed to assess whether the changes observed in otherwise healthy aged APOE4 mice are like those observed in human APOE4 carriers, and whether diet and psychosocial factors can contribute to cardiovascular and AD/dementia pathologies observed in the human population.

EFFECT OF APOE ϵ 4 STATUS ON PRECLINICAL COGNITION IN AUTOPSY CONFIRMED ALZHEIMER'S DISEASE. Ng W, Malek-Ahmadi M, Auman B, Belden CM, Berger J, Horner C, Arch A, Sakhai S, Evans B, Glass M, Moorley NR, Davis KJ, Cline CD, Serrano GE, Beach TG, A Atri. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Previous studies suggest neurocognitive performance varies between men and women and is moderated by the presence of the APOE ϵ 4 allele, a genetic risk factor for Alzheimer Disease (AD). Women with increased genetic risk were found to have lower scores on cognitive tests; those with two ϵ 4 alleles performed worse than men with two ϵ 4 alleles on delayed memory and the MMSE (Hobel et al., 2019). The relative risk of developing dementia between men and women remains controversial, though research consistently agrees that women are at increased risk in older age. Females with MCI due to AD have greater cognitive decline than males, especially when they were APOE ϵ 4 carriers (Sohn et al., 2018). Furthermore, females progressed to more severe AD pathology, with the highest Braak stage of neurofibrillary degeneration and neuritic plaque density (Filon et al., 2016). The literature regarding sex differences in cognitive performance consistently shows men with probable AD performed better on verbal memory, semantic fluency, and picture naming tasks compared to women with AD (Cieri et al., 2022; Irvine et al., 2012; Ryan et al., 2018). However, there are mixed results regarding executive functioning tasks, with some finding higher baseline performance in cognitively unimpaired (CU) women than men while another study found men to perform better on executive functioning tasks. In this study, we investigated sex differences in baseline neurocognitive performance and sought to determine whether carriage of the APOE ϵ 4 allele moderated this association.

Methods: Participants included 367 older adults with autopsy confirmed AD (Mbaseline = 81.24 ± 7.49 ; 64% female) who were considered CU at baseline. Autopsy confirmed AD was defined as participants with Braak stages III to VI, as well as moderate and frequent density of neocortical neuritic plaques. Participants completed annual neuropsychological testing through the Banner Sun Health Research Institute Brain and Body Donation Program (BBDP). Composite measures of memory, executive function, and language were used as dependent variables in linear regression models that adjusted for age and education. Main effects and interaction of sex and APOE ϵ 4 carrier status on composite domain scores were assessed.

Results: Regarding memory, APOE ϵ 4 carriers performed significantly worse than ϵ 4 non-carriers ($p = 0.01$) while there were no significant effects for sex ($p = 0.41$) or the sex by APOE ϵ 4 interaction ($p = 0.49$). No significant main effects or interactions were observed for executive function and language performance.

Conclusions: This study revealed no differential effect of APOE ϵ 4 carrier status on sex-related differences in memory, executive function, and language in a sample of older adults with autopsy-confirmed AD pathology who were cognitively unimpaired at baseline. The finding of lower memory performance among APOE ϵ 4 carriers is consistent with other studies, and further confirms its detrimental effects even in preclinical stages. However, our data did not find a sex-dependent effect of APOE ϵ 4 on cognition. It is possible that sex-specific APOE ϵ 4 differences in cognition manifest with the accumulation of AD pathology and are not apparent in the preclinical stages; thus, making it more difficult to detect AD in women.

EVALUATING TEMPLATE CREATION OF ADULT AND AGED BONNET MACAQUES.
Dieckhaus LA, McDermott KE, Gray DT, Comrie CJ, Hutchinson EB, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

Background: Template-based voxel wise analysis of brain MRI maps provides a bias-free way to examine population trends and to identify pathology these methods should be optimized to make them effective and robust. We acquired high resolution (200-600 micron isotropic) microstructural MRI in postmortem brains of adult (n=5) and aged (n=4) bonnet macaques. We used scans that contain microstructural information such as myelin and axon integrity (using multiple spin echo – MSE and Diffusion Tensor Imaging - DTI), large molecular densities such as aggregated proteins (using Selective Inversion Recovery – SIR) and iron content (using Multi- Gradient Echo). After processing our quantitative maps of interest including myelin water fraction (MWF from MSE), bound pool fraction (BPF from SIR) and fractional anisotropy (FA from DTI), we set out to compare these scans across specimens, which requires anatomically aligning specimens to each-other. A template was then constructed to obtain a standardized brain image that all individual brains from a cohort are mapped to. Templates can be created in various ways, but 2 common approaches are tensor based (which requires DTI) and scalar based (does not have a scan type requirement). However, the quantitative differences between these methods can lead to different interpretations of the data. An effective template ultimately allows the user to confidently run analyses and ask questions related to multiple specimens in their cohort in a less-biased manner.

Methods: We created a template from the nine bonnet macaque ex vivo brain specimens. Multiple MRI scan types were acquired, each having different contrasts among different brain structures. One template was created using a diffusion tensor-based method (diffeomorphic registration for Tensor Accurate Alignment of Anatomical Structures) and the other using diffeomorphic, multivariate scalar-based registration with the FA and Trace maps. To assess the quality of the registration in white matter, a region of interest (ROI) was created using a multivariate class open-source segmentation algorithm (ANTs atropos) on the FA tensor-based template and the FA-TR combined scalar-based template. We used the DICE coefficient, a similarity index which divides the overlap between the original scan and template by the values of both individually. For assessing the level of variance, an average FA map of each template was created and segmented for white matter. The average variance of FA, MWF, and BPF within the white matter mask was used to assess the variability in DTI and non-DTI map values.

Results: Scalar based template resulted in a DICE coefficient high of 0.75 and a low of 0.58 (+/- 0.065) while tensor-based template resulted in a DICE coefficient high of 0.84 and a low of 0.66 (+/- 0.051). MWF showed higher variance in the tensor-based method than scalar based (1,750.42 and 1,671.91 respectively). Both BPF and FA had a smaller variance in the tensor-based method to that of the scalar based (FA: 0.0027 and 0.003598, respectively; BPF: 1,157.96 and 1178.44, respectively).

Conclusions: Tensor-based template generation appears to be better suited for handling DTI maps and BPF maps for whole WM, but was associated with higher variance in the MWF maps suggesting that non-DTI metrics may be less reliable when using tensor-based templates. To further assess this, we plan to examine additional maps and single tract regions. It is possible that a hybrid approach of combining both templates or including additional metrics in the scalar-based template generation (not just FA and Trace) will provide improved template generations.

FIBRILLIN-1 MUTATION ACCELERATES CEREBROVASCULAR AGING AND INCREASES NEUROVASCULAR VULNERABILITY TO MILD TRAUMATIC BRAIN INJURY. Curry T, Barrameda ME, Bromberg CE, Saber M, Rowe RK, Gonzales RJ, Esfandiarei M, Currier Thomas T. University of Arizona College of Medicine-Phoenix; University of Arizona; Midwestern University; Barrow Neurological Institute at Phoenix Children's Hospital; University of Colorado Boulder; Arizona Alzheimer's Consortium.

Background: Age presents a significant risk for prolonged morbidity and mortality after traumatic brain injury (TBI), yet mechanisms associated with age-related cerebrovascular vulnerability following TBI remain unclear. Age induces transforming growth factor-beta (TGF- β) upregulation, implicated in cerebrovascular dysfunction, loss of blood-brain barrier (BBB) integrity, and increased neuroinflammation. Fibrillin-1 (Fbn1) mutation increases TGF- β availability and signaling in mice, inducing peripheral vascular dysfunction by 6-months (6M) of age. Patients suffering from Fbn1 mutation have increased risk of cerebrovascular complications such as stroke, aneurysm, and more severe outcomes after TBI, yet the effect on cerebrovascular function is unknown.

Methods: This study utilized male and female 6 and 12M old Fbn1 $^{+/-}$ and C57BL/6 wildtype (WT) mice to investigate the effect of Fbn1 mutation on accelerated vascular aging, cerebrovascular integrity, BBB permeability, and vulnerability to TBI. We hypothesized that Fbn1 mutation accelerates cerebrovascular aging, leaving the brain vulnerable to mild TBI (mTBI).

Results: Ultrasound imaging demonstrated that increased aortic root diameters and exacerbated aortic wall stiffness in Fbn1 $^{+/-}$ mice were associated with decreased posterior cerebral artery (PCA) blood flow compared to WT mice, similarly to 12M WT mice, which correlates with impaired PCA wall strength measured using isometric wire myography. To evaluate vulnerability to mTBI, fluid percussion injury was performed, where Fbn1 $^{+/-}$ mice required a 15% lower pressure to induce mTBI righting reflex times (5-10 minutes) compared to WT. Fluorescent microscopy of Evans blue extravasation, as well as brightfield imaging of ImmunoglobulinG staining demonstrated exacerbated BBB permeability in the hippocampus of 6M Fbn1 $^{+/-}$ mice compared to WT mice that were comparable to 12M WT and WT 1 day post injury (DPI) mice. This finding was further associated with increased iba-1 staining, suggesting elevated microglial activation. Higher neurological severity scale scores seen in 6M Fbn1 $^{+/-}$ mice suggests neurobehavioral alterations that were more like 12M WT and WT 1DPI mice.

Conclusions: These novel findings indicate that Fbn1 mutation and potentially its associated increase in TGF- β signaling accelerates vascular aging and alters cerebrovascular vulnerability to mTBI, where age-related modulation could be neuroprotective, and sex could be a determinant.

Funding-Valley_Research_Partnership-P1A-5012, NIH-R15HL145646, NIH-R01NS100793.

FLORBETAPIR PET MEASUREMENTS OF AMYLOID PLAQUE DEPOSITION ARE MORE CLOSELY CORRELATED WITH CROSS-SECTIONAL AND LONGITUDINAL COGNITIVE AND CLINICAL MEASUREMENTS USING A WHITE MATTER REFERENCE REGION OF INTEREST. Bhargava V, Wang M, Chen Y, Luo J, Weiner M, Landau S, Jagust W, Su Y, Reiman EM, Chen K. University of Arizona College of Medicine Phoenix; Banner Alzheimer's Institute; Arizona State University; Translational Genomics Research Institute; University of California San Francisco; University of California Berkeley; Arizona Alzheimer's Consortium.

Background: Quantification of the relationship between brain metabolism and amyloid deposition has been limited by variance in A β deposition measurements. We previously reported stronger statistical associations of FDG-PET measured glucose hypometabolism with A β deposition quantified using Standard Uptake Value Ratio (SUVR) with a cerebral white matter reference region-of-interest (SUVRwmRef) compared to the commonly used SUVR with cerebellar reference region-of-interest (SUVRcrblm) both cross-sectionally and longitudinally (Wang et al., AAIC 2021). The goal of this study was to compare cross-sectional and longitudinal associations of SUVRwmRef and SUVRcrblm with various cognitive/clinical measures.

Methods: Our study population consisted of 1133 participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) including 206 participants clinically diagnosed with AD dementia, 563 with Mild Cognitive Impairment (MCI), and 364 cognitively unimpaired individuals (CU). We computed partial correlation of SUVRwmRef or SUVRcrblm, covarying out baseline age and years of education, with: Mini Mental State Exam (MMSE); Sum Boxes, Clinical Dementia Rating Scale (CDR-SB); Alzheimer's Disease Assessment Scale (ADAS11, ADAS13); Auditory Verbal Learning Test – Short Term Memory, Long Term Memory, and Total (AVLT STM, AVLT LTM, and AVLT Total respectively). Steiger's Z-test was used to determine the SUVRwmRef and SUVRcrblm correlation coefficient differences with each of these cognitive/clinical measures at uncorrected $p=0.05$ significance. These analyses were carried out over all subjects and within each diagnostic group, first for baseline data and then longitudinally for changes of these measures.

Results: Cross sectionally, correlations were significantly stronger with SUVRwmRef than with SUVRcrblm for all subjects in all eight cognitive/clinical measures (Steiger's test, all $p < 7.6e-07$) with the strongest correlation of SUVRwmRef with ADAS13 (Pearson Correlation: $r=0.40$ for SUVRcrblm and $r=0.53$ for SUVRwmRef; Steiger's Test: $p=1.64e-19$). Within CU and MCI individuals, the strongest correlation of SUVRwmRef with ADAS13 was also observed (CU: $r=0.06$ for SUVRcrblm and $r=0.16$ for SUVRwmRef; Steiger's test $p=0.0013$; MCI: $r=0.29$ for SUVRcrblm and $r=0.34$ for SUVRwmRef; Steiger's test $p=0.0032$). The strongest correlation within AD subjects was found between SUVRwmRef and ADAS11 ($r=0.11$ for SUVRcrblm and $r=0.22$ for SUVRwmRef; Steiger's Test $p=0.0016$). Within AD individuals, correlations between AVLT STM and amyloid burden was not significant ($p=0.13$). Longitudinally, similar stronger SUVRwmRef correlations than SUVRcrblm with each of these cognitive measures were also observed.

Conclusions: Cerebral white matter reference regions for florbetapir PET demonstrate stronger and statistically significant associations between amyloid deposition and cognitive measures than results using cerebellar reference region. We conclude cerebral white matter reference region is superior to cerebellar reference region for amyloid PET analysis.

FUNCTIONAL CONNECTIVITY ACROSS VASCULAR SCALES IN ALZHEIMER'S DISEASE.

Keeling EG, Bergamino M, Sisco NJ, Ragunathan S, Quarles CC, Prigatano GP, Stokes AM. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: Functional connectivity can provide valuable insight into correlated activity across the brain. Decreases in functional connectivity begin to occur in normal aging and are hastened in Alzheimer's disease (AD). In particular, the default mode network (DMN), consisting of brain regions that increase in activity in the absence of a task, is of interest in AD due to its proposed functional role in memory consolidation and its anatomical overlap with amyloid burden. The DMN, along with the salience network (SN), are known to be impacted by AD. Although functional connectivity has frequently been assessed in AD, conventional functional MRI (fMRI) methods are dominated by macrovasculature, whereas microvascular data may be more reflective of AD pathology. To improve the sensitivity of resting-state fMRI methods in the context of AD, we implemented an advanced MRI method (termed spin- and gradient-echo (SAGE)) to assess functional networks, with complementary sensitivity to macro- and micro-vasculature, in a cohort of healthy aging and cognitively impaired adults. We hypothesize that this advanced method will yield unique and more robust resting-state networks across vascular scales compared to conventional methods. Additionally, we hypothesize that this method will more sensitively distinguish between groups than conventional methods.

Methods: The fMRI data were acquired at 3T (Ingenia, Philips) in two cohorts: (1) non-cognitively impaired cohort (HC, n=10, 70.8±6.6 years old, 7 females) and (2) cognitively impaired cohort, including both MCI and AD (CI, n=8, 74.0±6.2 years old, 4 females). Data were acquired with the SAGE acquisition (5 echoes with TE1-5=7.8/27/57/75/94 ms). Additional acquisition parameters were as follows: repetition time (TR) = 2.1 s, voxel size = 3×3×4 mm, 225 volumes, in-plane and through-plane acceleration, acquisition time = 7.88 min. SAGE-fMRI data underwent standard pre-processing. SAGE-based maps were calculated using log-linear fits. Independent component analysis (ICA) was run via MELODIC (FSL) for the macrovascular- and microvasculature-weighted SAGE maps, as well as for the conventional signals for comparison. Cohen's D effect size was calculated to assess group differences within components, where a threshold was set at medium size effect (D≥0.50).

Results: For DMN, SAGE macrovascular-weighted maps showed largely lateralized group differences, where the left and right posterior cingulate and left precuneus showed medium and large effect sizes (HC>CI) and the right posterior cingulate exhibited a large effect size (HC<CI); conventional DMN maps largely showed medium and large effect sizes (CI>HC) bilaterally within the precuneus, posterior cingulate, and medial prefrontal cortex. ICA did not result in a DMN component for microvasculature-sensitive contrasts. For the SN, group differences for microvascular-weighted SAGE showed a medium effect size (HC>CI) in the right insula and anterior cingulate. SAGE macrovascular group differences revealed a medium effect size (HC>CI) in the left and right insula. A smaller effect size was seen in the left and right insula for conventional SN maps, where HC<CI. ICA did not result in a SN component for the conventional microvascular signal.

Conclusions: Preliminary results show that SAGE may be able to more robustly identify resting state networks and more sensitively distinguish between healthy aging and cognitively impaired populations.

GLYPHOSATE INFILTRATES THE BRAIN AND INCREASES PRO-INFLAMMATORY CYTOKINE TNFA: IMPLICATIONS FOR NEURODEGENERATIVE DISORDERS. Winstone JK, Pathak KV, Winslow W, Piras IS, White J, Sharma R, Huentelman M, Pirrotte P, Velazquez R. Arizona State University; City of Hope Comprehensive Cancer Center; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Herbicides are environmental contaminants that have gained much attention due to the potential hazards they pose to human health. Glyphosate, the active ingredient in many commercial herbicides, is the most heavily applied herbicide worldwide. Much of the research on glyphosate exposure has focused on the peripheral and carcinogenic effects. The recent rise in glyphosate application to corn and soy crops correlates positively with increased death rates due to Alzheimer's disease and other neurodegenerative disorders, necessitating investigation of its effects in the brain. To this end, glyphosate has been shown to cross the blood–brain barrier in in vitro models but has yet to be verified in vivo. Additionally, reports have shown that glyphosate exposure increases pro-inflammatory cytokines in blood plasma, particularly tumor necrosis factor alpha (TNF α).

Methods: Here, we examined whether glyphosate infiltrates the brain and elevates TNF α levels in 4-month-old C57BL/6J mice. Mice received either 125, 250, or 500 mg/kg/day of glyphosate, or a vehicle via oral gavage for 14 days. Dosages were based off previous research examining the effects of exposure on anxiety-like behavior and locomotor function, and the highest dosage is below the No Observable Adverse Effect Level (NOAEL) established by the EPA. Urine, plasma, and brain samples were collected on the final day of dosing for analysis via Ultra-performance liquid chromatography – mass spectrometry (UPLC–MS) and enzyme-linked immunosorbent assays (ELISA). A subset of brain tissue underwent RNA sequencing (RNAseq) to determine changes in the transcriptome. Primary cortical neurons were derived from amyloidogenic APP/PS1 pups to evaluate in vitro changes in soluble A β 40 and 42 burden and cytotoxicity. To assess these changes in vivo, 4-month-old APP/PS1 mice and non-transgenic littermate controls were given either a vehicle, 50 mg/kg, or 500 mg/kg daily for four months via oral gavage. ELISAs for soluble and insoluble A β 40 and 42, oligomeric A β , and TNF α were performed on both hippocampal and cortical homogenates.

Results: Our analysis revealed that glyphosate infiltrated the brain in a dose-dependent manner and upregulated TNF α in both plasma and brain tissue post-exposure. Notably, glyphosate measures correlated positively with TNF α levels. RNAseq revealed over 200 differentially expressed genes in a dose-dependent manner and cell-type-specific deconvolution analysis showed enrichment of key biological processes in oligodendrocytes including myelination, axon ensheathment, glial cell development, and oligodendrocyte development. Glyphosate exposure in APP/PS1 primary cortical neurons increased levels of soluble A β 40 and 42 and cytotoxicity. Our in vivo APP/PS1 mouse study revealed that both soluble and insoluble A β 40 and 42 were elevated following chronic glyphosate exposure in the transgenic mice, but no difference in A β oligomers was detected. TNF α was significantly elevated in both transgenic and non-transgenic mice.

Conclusions: Collectively, these results show for the first time that glyphosate infiltrates the brain, elevates both the expression of TNF α and A β , and disrupts the transcriptome in a dose-dependent manner. Ongoing work in our lab is focusing on whether human relevant dosages of glyphosate produce similar effects in both normal and mouse models of Alzheimer's disease. In sum, exposure to this herbicide may have detrimental outcomes associated with brain-related functions for the general population.

HYPOACTIVITY PREDICTS APOE-E4 CARRIER STATUS AND ELEVATED TRIGLYCERIDE LEVELS IN A HUMANIZED APOE MOUSE MODEL OF ALZHEIMER'S DISEASE. McLean JW, Bhattra A, Vitali F, Raikes A, Wiegand JP, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.

Background: Alzheimer's Disease (AD) remains the largest contributor to neurodegenerative dementia worldwide. More than 95% of AD cases are idiopathic and influenced by several interacting risk factors. Age is the greatest risk factor for AD and the predominant genetic risk factor for AD is APOE- ϵ 4 carrier status. Additionally, women are nearly twice as likely to develop AD. This study investigates the impact of these risk factors upon behavior and metabolic biomarkers using the JAX mouse model of AD with targeted replacement of murine Apoe with human APOE- ϵ 3 or APOE- ϵ 4.

Methods: Male and female mice (total N=76; 23.27±1.21 months) underwent open field, novel object recognition (NOR), EchoMRI body composition analysis, peripheral metabolic and amyloid biomarker assays, and a subset (n=45) received 18F-FDG-PET imaging of cerebral glucose uptake. A Gaussian mixture model (GMM) cluster analysis based on behavioral parameters was used to identify similarly performing animals.

Results: GMM cluster analysis identified two distinct clusters. Cluster 1 was characterized by further distance traveled in open field (p=0.0016), familiarization (p<0.0001), and NOR (p<0.0001), compared to Cluster 2. Additionally, Cluster 1 animals exhibited greater object interaction time during both familiarization (p<0.0001) and NOR (p=0.0294). Interestingly, Cluster 1 had an equal distribution of APOE- ϵ 4 carriers and non-carriers while Cluster 2 had a significant overrepresentation of mice with at least one APOE- ϵ 4 allele (p=0.0375). The distribution of males and females did not differ between clusters. EchoMRI-based body composition analysis indicated no weight, lean tissue percentage, or adipose tissue percentage differences between clusters. However, males had greater total weight and lean mass compared to females within each cluster (both p<0.0001). Further, females had lower cerebral glucose uptake than males (p=0.0236). There were no sex or cluster effects in fasting blood glucose, ketone bodies, or plasma amyloid-beta (A β) levels. However, mice in Cluster 2 had elevated plasma triglyceride levels (p=0.0384).

Conclusions: These results suggest that both sex and behavioral performance clusters in aged humanized APOE mice differ in other AD-relevant parameters, including APOE- ϵ 4 carrier status, cerebral glucose uptake, body composition, and triglyceride levels. Differing bioenergetic profiles may precede cognitive changes in these mice leading to the behavioral clustering observed here, mimicking early clinical presentations of AD in humans.

INTEGRATING TRANSCRANIAL MAGNETIC STIMULATION AND ELECTROENCEPHALOGRAPHY AS AN APPROACH FOR STUDYING MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE. Hall JD, Green J, Chen AY, Chou Y-H. University of Arizona; Arizona Alzheimer's Consortium.

Background: The combined use of transcranial magnetic stimulation (TMS) with electroencephalography (EEG) has been shown to be a useful and informative method to better understand brain aging and age-related disorders such as mild cognitive disorder (MCI) and Alzheimer's Disease (AD). TMS-EEG is safe, well-tolerated, and non-invasive. This technique is unique in its ability to probe the underlying neurobiological processes that play a role in normative and non-normative (disordered) aging with temporal precision to the millisecond. The aims of this review are to summarize research findings of various TMS-EEG paradigms in MCI and AD and provide suggestions for the application of TMS-EEG for future research.

Methods: The databases selected to identify studies for inclusion in this meta-analysis were PubMed, ScienceDirect, and PsychInfo. Databases were searched using combinations of the following terms: "transcranial magnetic stimulation or TMS or theta burst stimulation or TBS", AND "encephalography or EEG", AND " Alzheimer's disease or AD or mild cognitive impairment or MCI". Studies were included if they met the following criteria: (1) clinical population of subjects previously diagnosed with MCI or AD; (2) use of a TMS-EEG protocol; and (3) articles written in English. Two authors (JH & JG) performed independent data extraction and any disagreements were resolved through joint discussion.

Results: Studies (n = 12) which evaluated characteristics of the TMS response with EEG reported significantly different temporo-spatial characteristics among individuals on the AD spectrum compared to healthy controls in corticospinal excitability, plasticity, and brain connectivity. Studies (n = 4) which further evaluated how characteristics of the TMS response correlated with cognitive outcome reported statistically significant correlations with various neuropsychological assessments such as the Mini-Mental State Examination, Montreal Cognitive Assessment, Alzheimer's Disease Assessment Scale-Cognitive Subscale, and Rey Assessment of Verbal Learning Test.

Conclusions: Findings of this review suggest that the integration of TMS and EEG has produced unique contributions to the understanding of the underlying neurophysiology of MCI and AD, and has great potential for diagnosis and prediction of treatment response. However, future works are needed to understand how the TMS-EEG paradigm can further optimize treatment in MCI and AD.

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

Background: Neural ensembles in the hippocampus and medial prefrontal cortex (mPFC) play a crucial role in spatial working memory, a process susceptible to decline during aging. These regions are connected via a monosynaptic, unidirectional projection from the ventral hippocampus (vHC) to the mPFC (Jay and Witter, 1991, *J. Com. Neurol.* 313:574), and damage or inhibition of this connection leads to impairments in spatial working memory tasks. Performance on spatial working memory tasks is known to correlate with increased synchrony of vHC theta (8-12 Hz) rhythms to mPFC neuron activity and is also coupled with mPFC local theta and gamma (30-100 Hz) oscillations. Additionally, the temporal offset of mPFC neurons phase-locking to vHC theta corresponds to the conduction delay between vHC and mPFC neurons, suggesting that the vHC-mPFC synchronization is a direct result of this projection. In the mPFC of aged rats, the frequency of gamma oscillations has been shown to be reduced. These gamma oscillations are known to result from an interaction between fast spiking inhibitory interneurons and their local excitatory neuron targets. The interactions between inhibitory and excitatory neurons are reduced by 1-2 msec in old rats. Little is understood about how monosynaptic vHC inputs engage mPFC, how this changes with age, or how vHC activation differentially affects neural activity along the dorsal-ventral axis of the mPFC.

Methods: To investigate these questions, we delivered electrical pulses to the CA1 layer of vHC in anesthetized male F344 young (9 months) and old (27 months) rats while simultaneously recording neural activity along the dorsoventral length of the mPFC using Neuropixels probes. Recordings were obtained from neurons spanning 5.5 mm along the mPFC, including the anterior cingulate cortex, prelimbic, and infralimbic regions (areas 24b, 32, and 25). Since vHC projections as well as general excitability characteristics are not uniform across the mPFC (Liu and Carter, 2018, *J. Neurosci.* 38:7351), we also compare neural activity across different layers of mPFC in response to vHC stimulation by recording from layer V and II/III in mPFC.

Results: This allows a comparison of the effects of direct vHC axonal input onto different layers and cell types within the three mPFC subregions recorded, as well as whether these connections are altered by aging.

Conclusions: This allows a comparison of the effects of direct vHC axonal input onto different layers and cell types within the three mPFC subregions recorded, as well as whether these connections are altered by aging.

INVESTIGATING THE CELLULAR MECHANISMS AND PHENOTYPIC EFFECTS OF THE APOE3 CHRISTCHURCH MUTATIONS IN AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE WITH ISOGENIC-BASED STEM CELL MODELS. Frisch C, Brafman D. Arizona State University; Arizona Alzheimer's Consortium.

Background: Genome-wide association studies have identified several genetic mutations involved in Alzheimer's disease (AD). Autosomal-dominant AD (ADAD) represents a genetically dominant inherited AD with mutations found in three genes: amyloid precursor protein (APP), presenilin 1 (PSEN1), or presenilin 2 (PSEN2). Sporadic AD is largely studied through polymorphisms present in the APOE gene that result in the three major isoforms: $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$. Regardless of AD type, pathology is represented through extracellular amyloid plaques and the formation of neurofibrillary tangles. A case study with an ADAD mutation PSEN1 E280A with a mutation identified in the APOE gene known as the APOE3 Christchurch (APOE R136S) mutation has exhibited no cognitive impairment with post-mortem brain studies revealing an excess of amyloid plaques with no tau pathologies when compared to patients with ADAD. Current advances in cellular models of AD overcome a variety of limitations seen in animal and post-mortem human models. Human-induced pluripotent stem cells (hiPSCs) are at the forefront of neurodegenerative disease research because of their ability to self-renew and differentiate into mature and functional cell types; however, studying mutation specific effects on disease phenotypes is confounded by genetic and epigenetic differences across various hiPSC lines. To limit these variables, this research aims to use an isogenic-based approach to understand the molecular mechanisms and phenotypic effects the APOE3 R136S mutation has on ADAD.

Methods: To overcome previous obstacles in genome editing of hiPSCs, prime editing with a transient reporter for editing enrichment was used to generate cell lines with the APOE3 R136S mutation and the PSEN1 E280A mutation in diseased and non-demented control hiPSC lines. With a dual guide RNA able to shift transmission of BFP to GFP and target the APOE3 R136S or PSEN1 E280A locus, hiPSCs were sorted for GFP positive cells and isolated to generate clonal hiPSC lines that acquire the respective mutation. These lines were characterized to ensure a normal euploid karyotype, pluripotency, trilineage differentiation potential, and an absence of off-target effects. Neurons and astrocytes are derived from the isogenic hiPSC lines using a scalable microcarrier-based differentiation protocol. Mutation specific effects will be determined through phenotypic assays, identification of signaling pathways, and identification of transcriptional targets.

Results: Using constructed vectors for the PE2, PE3, and PEmax systems, preliminary data shows the most efficient transient conversion and confirmed editing at the APOE3 R136S locus in an hiPSC line with a duplication in the APP gene with the PEmax system. The APOE3 R136S mutation has been confirmed with sanger sequencing and will go through extensive characterization to ensure normal euploid karyotype, pluripotency, trilineage differentiation potential, and an absence of off-target effects.

Conclusions: Upon completion of differentiations and experiments in hiPSCs, the isogenic-based approach will create an ideal cellular model to analyze the mechanistic effects that the APOE3 R136S mutation has on ADAD-related phenotypes and mechanisms.

INVESTIGATING THE PROTECTIVE MECHANISMS OF APOLIPOPROTEIN E2 (APOE2) IN MODULATING AMYLOID PRECURSOR PROTEIN (APP) PROCESSING. Srinivasan G, Frisch C, Raman S, Brookhouser N, Brafman DA. Arizona State University; University of Arizona College of Medicine-Phoenix; Arizona Alzheimer's Consortium.

Background: Apolipoprotein E (APOE) has been identified as a prominent risk factor for Alzheimer's disease (AD) with the E4 allele of APOE increasing the risk of AD 15-fold compared to APOE3. On the other hand, APOE2 has been suggested to decrease the likelihood of developing AD. However, the mechanisms by which APOE2 might exert such protective effects are unclear. This is specifically of interest, in the context of amyloid beta (A β) generation and clearance as an imbalance between the two processes has been hypothesized to drive AD pathogenesis. Here, we use a human induced pluripotent stem cell (hiPSC)-based model of AD to dissect the mechanisms by which APOE2 might modulate the processing of amyloid precursor protein (APP), which is proteolytically cleaved to form A β .

Methods: We previously generated APOE2 isogenic lines from APOE3 familial AD patient-derived hiPSCs using a cytosine base editor system and differentiated them to neurons and astrocytes in a microcarrier suspension culture system.

Results: Conversion of APOE3 to APOE2 resulted in preferential processing of APP in neurons by the non-amyloidogenic pathway that precludes A β generation. Lowered phosphorylation of APP, specifically at T668 in APOE2 neural cultures compared to APOE3 cultures suggest a role for differential APP phosphorylation in its processing. In addition, transcriptomic data revealed downregulation of key kinases that phosphorylate APP such as CDK5 and GSK3 β in APOE2 cultures. To investigate the effect of APP phosphorylation on its processing, we inhibited CDK5 and GSK3 β in our APOE isogenic neural cultures using small molecule inhibitors. Inhibiting these kinases had distinct effects on APP processing. While CDK5 inhibition lowered total and phosphorylated levels of APP as well as decreased both its amyloidogenic and non-amyloidogenic processing, GSK3 β inhibition did not lower the levels of phospho-APP but altered levels of amyloidogenic processing of APP.

Conclusions: Overall, inhibiting these kinases altered APP processing not strictly by lowering its phosphorylation and further studies probing APP localization, α -, β - and γ -secretase levels and activity would provide insight into the mechanisms by which this might occur. In the future, insights into these protective mechanisms of APOE2 would better inform therapeutics for AD.

LACK OF INTERACTION BETWEEN BDNF VAL66MET AND APOE E4 ON AMYLOID-PET, TAU-PET, HIPPOCAMPAL VOLUME, AND EPISODIC MEMORY IN COGNITIVELY UNIMPAIRED OLDER ADULTS. Shaw A, Malek-Ahmadi M, Devadas V, Wang Q, Su Y, Reiman EM. University of Nottingham; Banner Alzheimer's Institute; Arizona State University; University of Arizona; Arizona Alzheimer's Consortium.

Background: The interaction between the BDNF Met gene and APOE ϵ 4 gene on Alzheimer's disease (AD) pathology is not fully understood. We aimed to determine how this interaction impacts PET based Amyloid and Tau measurements, hippocampal volume, and Auditory Verbal Learning Tests (AVLT) in cognitively unimpaired (CU) older adults.

Methods: Data from 216 participants were used in this analysis. For the whole data set, the mean age was 75.56 ± 7.52 years, mean education was 16.82 ± 2.40 years, and 55% of the participants were female (118 females and 98 male). Linear regression models that adjusted for age, sex, education, were used to quantify main effects and interactions between APOE ϵ 4 carrier status and BDNF Met carrier status. Outcome measures included AV-45 Standardised Uptake Value Ratio (SUVR), tau meta-ROI, hippocampal volume, AVLT Delayed Recall, and AVLT Total Recall.

Results: There was a main effect on APOE ϵ 4 carrier status on amyloid load ($\beta = 0.11$, 95% CI (0.04, 0.17), $p = 0.001$), but no main effect for BDNF on amyloid load ($\beta = -0.003$, 95% CI (-0.06, 0.06) $p = 0.91$). The interaction between APOE ϵ 4 carrier status and BDNF Met carrier status was not significant ($\beta = 0.03$, 95% CI (-0.07, 0.13), $p = 0.58$). There was no main effect on APOE ϵ 4 carrier status on tau load ($\beta = 0.003$, 95% CI (-0.06, 0.06), $p = 0.93$). There was also no main effect on BDNF on tau load ($\beta = -0.0006$, 95% CI (-0.05, 0.05), $p = 0.98$) and the interaction between APOE ϵ 4 carrier status and BDNF Met carrier status was not significant ($\beta = 0.03$, 95% CI (-0.06, 0.12), $p = 0.49$). There were no significant main effects or interactions on hippocampal volume and cognitive measures.

Conclusions: This cross-sectional study found no significant interaction between APOE ϵ 4 carrier status and BDNF met carrier status on measures of amyloid and tau load as well as hippocampal volume and cognition. These findings cast doubt on the BDNF Met allele's role in moderating AD-related pathological changes.

LOOKING BACKWARD TO MOVE FORWARD: ON THE RELATIONSHIPS BETWEEN OVARIAN HORMONE LOSS, COGNITION, AND ANXIETY. Lizik C, Bernaud V, Peña V, Andrew K, Mitbander A, Bimonte-Nelson H. Arizona State University; Arizona Alzheimer's Consortium.

Background: The ovary is the main site of synthesis of steroid sex hormones, including estrogens, progesterone, and androgens. The rat ovariectomy (Ovx, surgical removal of the ovaries) model is established and widely used to study the impact of ovarian hormone deprivation on a myriad of reproductive and non-reproductive factors. These factors include brain and behavioral effects across the lifespan. There is abundant evidence that areas of the brain related to cognition and anxiety are sensitive to alterations in circulating ovarian hormones. The majority of this prior work, including our own, has focused on Ovx-induced cognitive changes.

Methods: The goal of the current experiment was to extend these findings of cognition to anxiety-like behaviors, and assess putative relationships amongst them. In this study, young adult female rats received either Ovx (n=9) or Sham (n=9) surgery, and were tested on spatial learning and memory tasks. Subjects were then also tested on the Elevated Plus Maze, which evaluates anxiety-like behaviors.

Results: Results showed cognitive impairments in Ovx rats, replicating the prior work of our and other laboratories. Anxiety-like behavioral data are being processed and analyzed. Moreover, relationships between anxiety markers and specific cognitive domains are currently being explored and will be presented at the poster session.

Conclusions: Since it has been established that these behavioral domains show changes with age and with hormone status, we hope that this work will be foundational to future studies evaluating interactive cognitive and affective questions across the lifespan from adulthood to aging in the female.

MIDDLE-AGED, GONADECTOMIZED RATS EXPOSED TO CHRONIC CORTICOSTERONE SHOW SEX DIFFERENCES IN HOW THEY RESPOND TO LONG-TERM 17BETA-ESTRADIOL TREATMENT ON SPATIAL WORKING MEMORY AND DEPRESSIVE-LIKE BEHAVIOR. Potus SS, Peay DN, Eir CC, Whittaker KE, Bandin E, Conrad CD. Arizona State University; Arizona Alzheimer's Consortium.

Background: Increases in stress coincide with depression and afflicts over 280 million people worldwide. Individuals with depression commonly exhibit loss of interest or pleasure (anhedonia) and often show other symptomology that can include, but are not limited to, diminished ability to think. Moreover, women are two-fold more likely to experience depression than men with estrogen being a key depressive- and cognitive-modulator. Our study aims to use a preclinical depressive-like model to identify whether estrogen can protect against cognitive impairment and depressive-like behavior in a middle-aged rat, an age that is highly susceptible to changes in estrogen. Both males and females were included to determine whether estrogen could have similar effects in both sexes.

Methods: Middle-aged (10 to 12 mos) male and female Fischer 344-cdf rats were gonadectomized and then randomly assigned to groups receiving stress hormone (corticosterone, CORT) or vehicle to produce a depressive-like phenotype and estrogen (17 β -estradiol, E2) or sesame oil. Rats were injected daily (s.c.), and then behavioral testing began on various tasks to assess depressive-like behavior, cognition (spatial working and reference memory), social interactions, and anxiety. My work focused on the spatial working memory using a water radial arm maze (WRAM) and depressive-like components (sucrose preference, SP) of the study. Testing began approximately three weeks into the CORT/E2 treatments and continued for two months. After two months of daily treatment, rats were euthanized and various tissues were collected for processing at a later date.

Results: For cognition, we found a significant estrogen and sex interaction on all measures of the WRAM. Females given E2 showed better spatial working and reference memory than compared to females given oil or males given oil or E2. Unexpectedly, CORT did not have an effect, but the data are being analyzed at different stages to determine whether differences may exist during acquisition, when rats are still learning the rules than compared to a plateau, when rats have acquired the rules and are performing at a stable rate. For SP, initial assessment for when sucrose is first presented, supports our prediction that CORT reduces SP in females compared to males, but final test assessment comparisons are pending.

Conclusions: Pertaining to cognition, the results are the first to show that middle-aged gonadectomized male and female rats respond to E2 and CORT differently. For WRAM performance, E2 improves spatial working and reference memory in females, but not in males. For males, E2 treatment failed to improve spatial working and reference memory and that performance was similar to oil-treated males and oil-treated females. For CORT treatment on cognition, no significant effects were found for spatial working or reference memory, but further analyses will be performed separately on the acquisition part of the learning curve and on the plateau when the rules were acquired. For depressive-like behavior, initial assessment supports our prediction that CORT treatment reduces SP in females compared to males with other comparisons pending. Future work will entail processing the brain tissue to understand the impact that E2 and CORT have on the prefrontal cortex, hippocampus, and amygdala, which all play a crucial role in the modulation of cognition and tend to be implicated in patients experiencing depressive-like symptomology. By understanding how estradiol impacts different neurological regions and chemical pathways of the brain during depressed and non-depressed conditions, more targeted pharmaceutical drugs can be developed to alter the cognitive dysfunction and anhedonia caused by depression. More importantly, the relationship between CORT and E2 at a cellular and behavioral level can allow us to tackle the vast array of symptoms that patients deal with on a daily basis.

MRI SIGNATURES OF BRAIN AGE IN THE ALZHEIMER'S DISEASE CONTINUUM. Shah J, Ghisays V, Chen Y, Luo J, Li B, Reiman EM, Chen K, Wu T, Su Y. Arizona State University; Mayo Clinic Arizona; Banner Alzheimer's Institute; University of Arizona; Arizona Alzheimer's Consortium.

Background: Age is the biggest risk factor for Alzheimer's disease (AD). Substantial efforts to extract age signatures from magnetic resonance imaging (MRI) of the brain have achieved impressive accuracy and demonstrated these signatures were altered by neurological disorders including AD. In this work, we develop a deep learning model to characterize brain age signatures and examine their variation over the AD continuum.

Methods: A 3D deep ResNet model was implemented to learn the structural signatures of brain age in predicting the chronological age of the participants. The model was trained on 7372 T1-weighted MRI scans from a combined lifespan cohort of 5848 cognitively normal participants (age: 8- 95 yrs) using a 10-fold cross validation procedure. The model was then applied to the independent ADNI cohort (N=1175, 50-98 yrs) to examine MRI derived brain age signatures variation in the AD continuum. The difference (Δ age) between model predicted age and chronological age was used as the independent variable for group comparison using univariate ANCOVA tests, controlling for sex, education, and APOE4 gene dose, among five clinical groups: normal control (NC), normal to MCI converters (NC-MCI), stable MCI (MCIs), MCI to AD converters (MCI-AD), and AD patients.

Results: The ResNet model achieved an MAE=3.76 yrs and R2=0.93 across 10 folds in the lifespan cohort. In the baseline data of the ADNI cohort, model derived Δ age increased along the AD continuum as expected: NC (-1.2yrs) < NC-MCI (-0.7yrs) < MCIs (-0.3yrs) < MCI-AD (0.7yrs) < AD (1.5yrs) (F=11.24, p<0.0001). Post-hoc pairwise comparison results are summarized in Table 1/Figure 2. Although the difference between NC and NC-MCI did not reach significance (p=0.24) for the baseline data, comparison between the two groups using data from all visits was significant (p=0.0009), suggesting more subtle differences.

Conclusions: A ResNet model was developed that captures the MRI signatures of brain age with high accuracy in age prediction. The model detected group level differences along the AD continuum in the expected direction. Subtle changes in brain signatures were observable in normal participants who later developed cognitive impairment. Our technique provides a novel approach to investigate the relationship between aging and AD.

NEURODEGENERATION BIOMARKERS IN A PRECLINICAL MODEL OF VASCULAR DEMENTIA AND CLINICAL STUDIES OF HEART DISEASE INDIVIDUALS AT RISK FOR VASCULAR COGNITIVE IMPAIRMENT: EFFECTS OF TREATMENT WITH ANGIOTENSIN-(1-7). Hoyer-Kimura C, Konhilas J, Ryan L, Hay M. University of Arizona; Arizona Alzheimer's Consortium.

Background: Neurofilament light protein (NfL) and pTau are established biomarkers of neurodegeneration in both Alzheimer's disease (AD) and Alzheimer's Disease Related Dementias (ADRD). Our team has completed preclinical studies of vascular contributions to cognitive impairment and dementias (VCID) that show that both cognitive impairment and NfL are decreased following 3-weeks treatment with Angiotensin-(1-7) (Ang-1-7) agonists. We have begun translating these studies to human clinical trials in heart failure (HF) subjects and patients undergoing cardiac surgery who are at risk for VCID/ADRD.

Methods: Preclinical- HF was induced in C57Bl/6J adult male mice by myocardial infarction (MI) (n=15); control mice underwent sham surgeries (n=10). 5 weeks following MI, mice were treated with Ang-(1-7) agonist s.c. injections (0.5-500 micrograms/kg/day) for 21 days. Following treatment, cognitive function was measured by novel-object recognition (NOR) and plasma and brain samples were obtained upon sacrifice. Plasma NfL was measured using Simoa Quanterix and brain inflammatory cytokines measured with Milliplex assay. Statistical analysis was performed using GraphPad using t-test, and Pearson r correlation. Clinical- (1: HF) Serum samples were obtained (NHLBI BioLINCC) from 58 participants of a previously completed TOPCAT trial, were >50 years of age, had symptomatic HF categorized (52% female). Aged-matched control serum samples were obtained with no known health issues (n=24, 50% female). Serum NfL and pTau181 were measured using Simoa Quanterix. Clinical- (2: CABG) In a small pilot study in five cardiac bypass patients, three received 21days of 200 micrograms/kg/day s.c. of Ang-(1-7) and 2 received saline placebo. Cognitive function and NfL were measured prior to surgery and at 21 and 90-days post-surgery.

Results: Preclinical- HF mice had significant cognitive impairment (decreased discrimination ratio in NOR, $p < 0.05$) and a significant increase in plasma NfL levels in comparison to control mice. NfL levels were significantly correlated with NOR test scores ($r = -0.43$, $p = 0.03$) and changes in brain anti-inflammatory biomarkers ($r = -0.52$, $p = .001$). Treatment with Ang-(1-7) agonists reversed the cognitive impairment and NfL levels and increased protective brain cytokines. Clinical- (1: HF) Baseline NfL levels and pTau181 were significantly higher in NYHA class I/II (n=31) and III/IV (n=27, $p < .0001$) than in age-matched controls. After 12-months, participants in NYHA class I/II had an increase in NfL of $9.6 \pm 5\%$ relative to baseline and those in class III/IV had a $31.7 \pm 17\%$ increase from baseline. Clinical-(2:CABG) In a pilot study, NfL was increased in all cardiac bypass patients relative to healthy controls pre-surgery. Treatment with Ang-(1-7) for 21 days post-surgery (n=3) showed improvement in cognitive function and decreased NfL levels as compared to saline-placebo controls (n=2). There were no adverse effects of the peptide therapy.

Conclusions: These results demonstrate that 1) Ang-(1-7) reverses cognitive impairment and reduces NfL levels in a preclinical model of VCID, 2) VCID-at risk HF subjects have elevated levels of NfL and pTau181, and 3) treatment with Ang-(1-7) may prevent cardiac surgery induced cognitive impairment and decrease neurodegeneration biomarkers. (Supported by NIA U01AG066623, NHLBI BioLINCC and ACC.)

NEURODEGENERATIVE EFFECTS FOLLOWING A UNILATERAL TRAUMATIC BRAIN INJURY. Bjorklund GR, Wong J, Brafman D, Stabenfeldt SE, Bowser R. Arizona State University; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: A vast majority of age-related neurodegenerative diseases (NDDs) have no familial or genetic basis and are considered sporadic in nature due to complex genetic and environmental factors. For example, Alzheimer's disease (AD) occurs sporadically in over 90% of cases, approximately 60-70% of frontotemporal dementia (FTD) cases are sporadic, and amyotrophic lateral sclerosis (ALS) occurs sporadically in 90-95% of cases. Of the several environmental factors that lead to a higher risk of developing NDDs include brain injuries which are increasingly associated with the future development of NDDs such as AD, FTD, and ALS.

Methods: In this investigation, we examined tissue samples from the rodent forebrain and spinal cord following a unilateral traumatic brain injury (TBI) centered over the primary and secondary motor cortices. Cortical tissue analyzed used both ipsi- and contralateral areas of the cortical forebrain separate from the injury site and the functionally connected cervical spinal cord. Animals used were wild-type C57BL/6J mice with no genetic predisposition to neurodegenerative disease. Analysis time points used were 7, 14-, 28-, 120-, and 180-days post injury (DPI) in order to determine short- and long-term cellular neurodegenerative effects as well as the possibility that any detected effects may resolve over time. For the immunohistochemistry analysis, we used TDP-43 nuclear mislocalization in RBFOX3 positive cells as the primary neurodegenerative marker. TDP-43 pathologies are detected in up to approximately 70% of AD cases, approximately 50% of FTD cases, and are considered a hallmark of ALS seen in up to 97% of cases. This analysis assessed the total number of cells that immunostained positive for RBFOX3 and that also displayed indications of TDP-43 nuclear mislocalization. RNAseq analysis was then used to identify differentially expressed genes and transcriptome profiles of affected biological processes following a TBI at equivalent time points. All results were compared to naive age-matched animals using anatomically matched regions.

Results: Immunostaining results for TDP-43 nuclear mislocalization in RBFOX3 positive cells revealed significant increases at the 7, 14, 28, and 180 DPI timepoints when compared to naïve controls. The results also showed significant increases over time from each of the analyzed time points to 180 DPI. Further analysis shows this increase progress in a layer-wise manner expressing more prominently in the upper layers of the cortex followed by the deeper layers of the cortex over time. Preliminary RNAseq analysis detected an extensive increase of differentially expressed genes (DEGs) over the analyzed time points in the cortical forebrain when compared to naïve controls. The cervical spinal cord however showed far fewer DEGs with the largest increase seen in the downregulated DEG set. A striking result seen is the lack of overlap in DEGs over the analyzed time period in both the forebrain and spinal cord for both upregulated and downregulated DEGs. Ontology analysis identified several significantly represented biological processes implicated in candidate pathways that contribute to neurodegeneration. These processes include signal transduction, response to stress, response to stimulus, regulation of gene expression, regulation of RNA processes, and establishment of localization.

Conclusions: Our results indicate a significant increase in both cortical and cervical RBFOX3 positive cells that display TDP-43 nuclear mislocalization following a unilateral TBI when compared to uninjured age-matched controls over time. We further found that DEGs increased dramatically over time with little to no overlap between early and late timepoints. Biological process ontologies represented by the sets of DEGs include candidate pathways that contribute to neurodegeneration. Together, these results indicate an increasing pattern of neurodegenerative effects over the time course analyzed following a TBI.

NEUROINFLAMMATORY PROFILES OF THE HUMAN FEMALE BRAIN AT MIDLIFE RESEMBLES THE HUMAN MALE LATE-LIFE ALZHEIMER'S BRAIN. Delatorre N, Van Rossum H, Mishra A, Padilla-Rodriguez M, Rodgers K, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.

Background: Neuroinflammation is a well-documented feature of Alzheimer's Disease (AD). Two important questions in defining the role of the neuroimmune system in AD remain unaddressed: 1) the initiation phase of inflammation and 2) sex differences in the inflammatory cascade. Previous preclinical findings from our group demonstrated elevated inflammatory and immune transcripts including CD3, CD4, and MHCII. With this work, we extend and translate our preclinical discoveries to test the hypotheses that the inflammatory phenotype of LOAD is initiated in midlife of the human aging process and sex differences are prevalent.

Methods: Both fixed and frozen human tissue samples were obtained from NIH NeuroBioBank (University of Maryland, University of Miami, and Mt. Sinai) that included the corpus callosum, hippocampus, and hypothalamus of 40 brain donors that were sex and age matched. For the purposes of this study, samples were sub-classified into 3 groups: healthy aging 40-49 years-old, healthy aging 50-59 years-old, and AD age 60-80 years-old. Transcriptomic analyses were conducted to determine neuroinflammatory gene expression and to identify common signaling profiles. Neuroinflammatory markers were visualized using 3,3'-diaminobenzidine immunohistochemistry and included microglia (IBA-1), activated microglia (HLA), and T-cells (CD3, CD4, CD8).

Results: Gene expression change was determined by comparing each group to the young male. The profiles were compared using fisher exact tests and revealed region-specific and sex-specific transcript regulation. Midlife females showed significant differences in genes involved in hypothalamic adaptive immune response ($p=0.0054$), hippocampal astrocyte function $p=0.007$, and hypothalamic inflammatory signaling $p=0.028$). AD males exhibited altered gene expression in corpus callosum neurotransmission ($p=0.0355$), hippocampal innate immune response, and hypothalamic adaptive and innate immune response ($p=0.0496$, $p=0.0208$). Both midlife female and AD male exhibited hippocampal upregulation of innate immune transcripts and hypothalamic upregulation of adaptive and innate immune response genes.

Conclusions: These results provide evidence of early activation of the immune response in brain as a potential sex-dependent risk factor for AD. Outcomes of these analyses support future studies that identify neuroimmune biomarkers of the AD prodrome and present an early opportunity for intervention in order to reduce risk and or delay AD.

NOISE2DWI: A SELF-SUPERVISED DEEP LEARNING METHOD FOR ACCELERATED DIFFUSION TENSOR IMAGING. Martin P, Altbach M, Bilgin A. University of Arizona; Arizona Alzheimer's Consortium.

Background: Diffusion tensor imaging (DTI) is a diffusion-weighted magnetic resonance imaging (dMRI) technique utilized to quantify and assess microstructural characteristics in tissue. DTI is used to study an extensive array of physiological and structural processes in neuronal connectivity. One drawback of DTI is the long acquisition times required to obtain a large number of diffusion-weighted images (DWIs) for accurate estimation of the diffusion tensor. Recently, fully-supervised deep learning (FSDL) techniques have been introduced to overcome the limitations of DTI. Unfortunately, these techniques require large amounts of high-quality DWI data for training. In this work, we present a novel self-supervised deep learning (SSDL) framework, Noise2DWI, which relaxes the requirement of large training datasets.

Methods: For this work, we compared our SSDL framework with a FSDL method. The FSDL model involved taking $k = 6$ and $k = 12$ noisy DWIs, together with a single $b=0$ image, as input. For obtaining the labels, tensor fitting was performed using 90 DWIs and the fitted tensor was used to generate denoised images along the first k diffusion directions using MRtrix software. These k denoised DWIs were used as labels during fully-supervised training with mean absolute error (MAE) loss. The SSDL processing consists of pre-training with self-supervision followed by fully-supervised fine-tuning on a small number of datasets. During self-supervised pretraining, the same number of k noisy DWIs from 50 subjects were used. The noisy samples were used as labels. The inputs to the network were generated by randomly replacing a small fraction of the pixels in each training sample with noise. A custom loss function was implemented to compute mean absolute error only on the replaced pixels. During the fine-tuning stage, the encoder weights of the pre-trained network were frozen, and the decoder weights were fine-tuned using fully-supervised training with DTI-denoised data comprised of 1,2, and 4 subjects.

Results: Our results demonstrate that self-supervised pre-training followed by fine-tuning on 1, 2, and 4 labeled datasets can yield performance similar to or better than fully-supervised training on a cohort of 50 subjects. This is particularly true at high acceleration rates, such as $k = 6$ DWIs.

Conclusions: We have demonstrated a novel SSDL technique, Noise2DWI, which enables high-accuracy predictions of DTI metrics from accelerated acquisitions. Noise2DWI can learn from accelerated acquisitions, significantly reducing the requirements of the number of datasets with high directional encodings, which are needed for full-supervised training.

NOVEL ALLOSTERIC NAD ENHANCEMENT TO SUPPORT NEURAL RESILIENCE IN ADRD.
Krider IS, Ratia KM, Shen Z, Laham M, Ackerman-Berrier M, Penton C, Knowles NG, Reddy MS, Reddy VG, Xiong R, Fu J, Thatcher GRJ. University of Arizona; University of Illinois at Chicago; Arizona Alzheimer's Consortium.

Background: Aging is the single most significant risk factor for Alzheimer's disease and related dementia (ADRD), leading to consideration of new therapeutic approaches, such as nicotinamide adenine dinucleotide (NAD⁺) enhancing dietary supplements that exhibit anti-aging properties and improve lifespan and healthspan in rodents. A decline in the NAD pool plays a crucial role in the aging brain, by increasing mitochondrial dysfunction and various age-related pathologies including enhanced oxidative stress, inflammation, and impaired insulin sensitivity. Maintaining levels of NAD, a central metabolic cofactor in eukaryotic cells that plays a critical role in electron transfer, cellular metabolism, and energy homeostasis, relies in mammals on the salvage of nicotinamide (NAM) by the enzyme nicotinamide phosphoribosyltransferase (NAMPT). NAD is catabolized to NAM by PARPs, SIRT6, and CD38; systems that are upregulated to counteract DNA damage and cellular stress with aging. We have discovered a unique NAMPT positive allosteric modulatory mechanism, supported by co-crystal structures of NAMPT positive allosteric modulators (N-PAMs). We hypothesize a N-PAM that selectively activates NAMPT in the brain, increasing NAM turnover and attenuating ATP consumption, will ameliorate the age-related loss of NAD that combines with AD pathology in the pathogenesis ADRD.

Methods: Candidate N-PAMs were discovered using an HTS coupled-enzyme assay and validated with orthogonal biochemical assays, with a focus on physicochemical properties driving brain bioavailability. Three hit series have been identified with nanomolar-to-micromolar potency and affinity and NAMPT co-crystal structures were obtained. Cell-based assays were used to confirm elevation of NAD levels in response to N-PAM treatment. The primary assay of NAMPT enzyme activity measured NAD⁺ production by coupling the NAMPT-catalyzed production of NMN with the conversion of NMN to NAD⁺ catalyzed by nicotinamide/nicotinic acid mononucleotide adenylyltransferase (NMNAT); and alcohol dehydrogenase (ADH) and DT-diaphorase. A fluorescence-polarization (FP) probe was developed to confirm and quantify affinity of N-PAMs for NAMPT along with microscale thermophoresis (MST) measurements.

Results: Through the HTS campaign, a novel class of N-PAMs was discovered in addition revealing NAMPT activation by biogenic and/or bioactive phenols. The mechanism of activation was revealed through synthesis of chemical probes, supported by co-crystal structures. Binding to a rear channel in NAMPT regulates NAM binding and turnover, with biochemical observations being replicated by NAD⁺ measurements in human cells. For the N-PAMs, the biochemical observations on NAMPT activation translated to modulation of NAD⁺ in a cellular context, despite the cellular NAMPT feedback-inhibition expected for NAM and NAD⁺.

Conclusions: Differentiation was observed in multiple responses to N-PAMs compared to other reported NAMPT activators, including dependence on ATP and NAM concentration and modulation of the uncoupled ATPase reaction of NAMPT. The identification of differentiated classes of activators indicates that the dependence of NAMPT activity on cellular concentrations of substrates, products, and related metabolites can be regulated by design. Pharmacological activation of NAMPT in metabolic disorders, diseases of aging, and ADRD to elevate levels of cellular NMN and NAD⁺ levels, is a promising therapeutic strategy.

PROGRANULIN PROCESSING AND GROWTH RESPONSE IN SW13 CELLS: POTENTIAL LINKS TO LYSOSOMAL FUNCTION AND NEURODEGENERATIVE DISEASE. Biparva P, Pascual AS, Montgomery MR, Leyva KJ, Hull EE. Midwestern University; Oklahoma State University; Arizona Alzheimer's Consortium.

Background: Progranulin (PGRN) is a pleiotropic signaling molecule composed of 7.5 granulin repeats, regulating many diverse biological processes including cellular proliferation, inflammation, tumorigenesis, and lysosome function. Mutations in the PGRN gene are implicated in causing neurodegenerative diseases such as frontotemporal lobar degeneration, neuronal ceroid lipofuscinosis, and Alzheimer's disease, yet the mechanisms by which PGRN promotes neuronal health are unclear. A key determinant affecting PGRN activity is proteolytic processing of PGRN into various granulin subunits, with lysosomal pH influencing protease activity. The SW13 human adrenal carcinoma cell line, which exists in two epigenetically distinct subtypes (SW13+ and SW13-), addresses the link between lysosomal pH and PGRN processing. Previous results showed that SW13+ cells express higher amounts of PGRN than SW13- cells, yet only SW13- cells respond to PGRN by increasing their growth rate. These subtypes also appear to differ in lysosomal pH. Thus, the SW13 cell line is a uniquely powerful tool to address the link between granulin function and lysosomal pH.

Methods: To determine lysosomal pH of SW13+ and SW13- cells, each subtype was cultured and pH of the cellular lysosomes was determined by incubating the cells with a lysosensor dye (DND-160 or DND-189), then measuring fluorescent intensity of the lysosomes. Fluorescent intensity was compared to a standard curve to determine pH. To establish if there are functional differences in lysosomes from SW13+ and SW13- cells, lysosomes were isolated and purified using density gradient centrifugation. Purified lysosomes from each subtype were analyzed via immunoblotting to determine expression levels of lysosomal-associated membrane protein 1 (LAMP1) and granulin units. Data were analyzed using a non-parametric Mann-Whitney test with an alpha level of 0.05.

Results: Suggestive of altered lysosomal function, preliminary results suggest that LAMP1 expression varies between the SW13 subtypes. Consistent with altered lysosomal processing of PGRN and immunoblotting using antibodies specific for various granulin units, we determined that SW13- cells produce higher amounts of granulin-4, which has pro-growth activity, than SW13+ cells. Conversely, SW13+ cells produce more granulin-3, which has been shown to inhibit growth. Evidence supporting this differential processing can be seen in the response to the addition of PGRN. Specifically, different concentrations of PGRN are required to stimulate growth in the SW13 cell subtypes, with SW13+ requiring higher amounts than SW13-. Taken together, these data suggest that PGRN may be a prominent epigenetic factor involved in subtype switching. Further immunoblotting for additional granulin units will further elucidate differences in PGRN processing in the SW13 subtypes.

Conclusions: These data support a role for lysosomal processing of progranulin and may have implications for the treatment of several neurodegenerative diseases. Ongoing experiments are aimed at probing the ability of altered lysosomal pH to generate differential processing of progranulin.

REAL-WORLD GOAL SETTING AND FOLLOW THROUGH IN YOUNG AND OLDER ADULTS.

Lauren E. Cruz LE, Christopher X. Griffith CX, Cegavske C, Burns H, Andrews-Hanna JR, Grilli MD. University of Arizona; Arizona Alzheimer's Consortium.

Background: The ability to generate, plan for, and follow through with goals is essential to everyday functioning. Compared to young adults, cognitively normal older adults have more difficulty on a variety of cognitive functions that contribute to goal setting and follow through, including episodic future thinking. However, how these age-related cognitive differences impact real-world goal planning and success remains unclear. In the current study, we aimed to better understand the impact of older age on everyday goal planning and success.

Methods: Cognitively normal young adults (18-35 years, $n = 57$) and older adults (60-80 years, $n = 49$) participated in a two-session study spanning 10 days. In the first session, participants described 4 real-world goals that they hoped to pursue in the next 10 days. These goals were subjectively rated for personal significance, significance to others, and vividness. Ten days later, participants rated the degree to which they planned for and made progress in their real-world goals since session one. They also completed the self-report prospective and retrospective memory questionnaire (PRMQ), among other surveys. Older adults also completed a battery of neuropsychological tests.

Results: Relative to the young adults, cognitively normal older adults described real-world goals that they perceived as more important to other people ($p = 0.032$), and they reported more goal planning during the 10 day window ($p < 0.001$). There was not a statistically significant age group difference, however, in real-world goal progress. Nonetheless, within the older adult group, more goal planning during the 10 day window was associated with more goal progress ($r = 0.42$, $p = 0.002$). Also, among young adults, individuals who reported less difficulty with their daily prospective memory on the PRMQ tended to engage in more goal planning ($r = -0.28$, $p = 0.03$). Interestingly, this planning was not associated with increased goal progress in younger adults ($r = 0.21$, $p = 0.13$). Across the entire sample, real-world goals that were imagined more vividly also tended to be more personally significant ($r = 0.337$, $p < 0.001$). Within the older cohort, those who scored lower on the Rey Complex Figure Test (RCFT) long delay recall trial reported that their goals were more similar to ones that they had set in the past ($r = -0.34$, $p = 0.02$).

Conclusions: Although older adults tend to show decline in several cognitive domains relevant to goal setting, we found that cognitively normal older adults did not make significantly less progress toward a series of real-world goals over a 10-day window. However, relative to young adults, older adults tended to pursue more socially-oriented goals. Older adults also appear to rely on planning more than young adults to make progress toward their goals, and older adults with lower episodic memory may pursue more habitual goals. While younger adults with better prospective memory engaged in more planning, their planning was not shown to correlate with increased goal progress. These findings are in line with prior research suggesting that cognitive aging effects may be more subtle, or non-existent, when assessed in real-world contexts.

STATIN RESPONDER ANALYSIS FOR PRECISION PREVENTION OF ALZHEIMER'S DISEASE. Torrandell-Haro G, Branigan GL, Rodgers KE, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.

Background: Previously we identified reduced risk of Alzheimer's Disease (AD) in statin users (Torrandell-Haro et al. 2020). Identifying the subgroup of responders is an important step towards a precision statin therapy approach. This study aimed to investigate the effect of statin therapy on the incidence of Alzheimer's Disease (AD) and other age-related neurodegenerative diseases (NDD) by therapy, sex, and age group. Moreover, it sought to identify and describe responder vs non-responder phenotypes to statin therapy based on demographic characteristics, comorbidity burden, and drug exposure.

Methods: A retrospective analysis was conducted using a US-based insurance claims dataset of 53 million participants. Inclusion criteria included participants aged 45 years old or older, with no prior history of NDD before statin use, and with claims enrolled for at least 6 months prior and 3 years after start of statin therapy. A propensity score-matched based on age, gender, region, comorbidities and cci was applied for group assignment. Records were surveyed for a diagnosis of AD 1 year after statin exposure. Sensitivity analyses for the detection of responders based on comorbidities and drug combinations were conducted.

Results: Of the 1,293,952 participants who met inclusion criteria, 646,976 participants were exposed to statin therapy and were propensity score-matched to 646,976 patients without exposure. Statin use was associated with a decreased risk of AD (RR [95% CI]: 0.50 [0.48–0.52]; $P < .001$) and other NDD. Additionally, men exhibited a greater risk reduction than women for non-AD dementia. Responders had a higher incidence of obesity and asthma whereas non-responders were predominantly female and had an overall higher incidence of cardiovascular and cerebrovascular comorbidities.

Conclusions: Statin use was associated with a reduced risk of AD and other NDD, replicating previous results. Non-responders were predominantly women with a high incidence of cardiovascular comorbidities. Characterization of responders to statin exposure advances a precision prevention approach, in which prescription guidelines consider neurological health and are adapted for at-risk populations.

SYSTOLIC BLOOD PRESSURE AND LONGITUDINAL WHITE MATTER HYPERINTENSITY DATA FROM TWO STUDIES TO INFORM THE DESIGN OF AN ANTI-HYPERTENSIVE PREVENTION TRIAL IN MIDDLE-AGED ADULTS. Nichols JB, Chen Y, Chen K, Su Y, Tsai P, Reiman EM, Alexander RC, Tariot PN, Pruzin JJ. Banner Alzheimer's Institute; Midwestern University; Arizona State University; University of Arizona; Arizona Alzheimer's Consortium.

Background: Midlife vascular risk factors, especially hypertension, confer an increased risk for future Alzheimer's disease dementia. White matter hyperintensity volume (WMHV) is a means of quantifying small vessel disease on MRI and correlates closely with cognitive symptoms and higher risk of future decline. The SPRINT research group demonstrated a systolic blood pressure (SBP) goal of <120 mm Hg to lower the risk of combined MCI/dementia by ~15% in older adults and to prospectively lower WMHV compared to a goal SBP<140 mm Hg (SPRINT Investigators 2015, 2019, 2019). Since it is still unknown if lowering SBP would confer greater benefit when implemented at a younger age, we are proposing a prospective clinical trial in which middle-aged participants (aged 45-69) with baseline SBP≥132 mm Hg are randomized to a more intensive SBP goal (<120 mm Hg) and compared to a 'usual care' group (estimated average SBP≥135 mm Hg) with longitudinal accumulation of WMHV as the primary outcome. Using existing data, we report SBP achieved by 'usual care,' describe baseline existing WMHV by SBP, estimate annualized rate of change for WMHV, and conduct a power analysis for the potential trial.

Methods: We requested and obtained preliminary data from the Wisconsin Registry for Alzheimer's Prevention (WRAP) and from SPRINT clinical trials. WRAP is an ongoing observational cohort study that started enrolling in 2001, currently with 123 participants aged 45-69 with at least two MRIs and SBP data available over 2.4 years. The SPRINT trial enrolled 5,366 participants aged 50-69, a subset of 417 participants who also had longitudinal MRI data from two visits over 3.9 years. We describe average SBP and baseline WMHV (values provided by individual studies). We next used a linear mixed effects model to estimate the annualized rate of change of WMHV for the WRAP data. With the SPRINT data, we used the simple subtraction method (with the caveat discussed in Chen et al., 2022) to estimate the annualized rate of change of WMHV and to perform the statistical power analysis at a 2-sided significance level of 0.05 with 80% power for a trial lasting four years.

Results: SPRINT trial participants aged 55-69 had a mean baseline SBP of 138.6 mm Hg. Mean SBP in WRAP for participants aged 45-69 with a baseline SBP ≥ 132 was 143 mm Hg. In both SPRINT and WRAP, the majority of participants had at least 0.25cm³ of WMHV at baseline (98.8% and 55% respectively). The mean baseline WMHVs were 4.42cm³ for SPRINT and 0.74cm³ for WRAP. Annualized rate of change of WMHV for the 17 participants with sufficient data was 0.101 ± 0.179 cm³ per year (mean follow up 2.41 years). The annualized rate of change in SPRINT was 0.22 ± 0.70 (n=157) in the goal SBP <120 mm Hg group, compared to 0.40 ± 0.7 (n=150) in the goal SBP <140 mm Hg group. Power analysis using SPRINT data estimated the required sample size to be 239 participants per arm for the trial proposed.

Conclusions: In these data sets, most middle-aged people have some degree of existing WMHV and those with hypertension have an SBP controlled to an average of about 140 mm Hg, thus making the proposed trial broadly applicable and generalizable. These data also suggest that intensive SBP control will slow the rate of WMHV accumulation in middle age, possibly reducing risk for future dementia. Two key limitations are that different techniques were used to quantify WMHV limiting direct comparison, and the populations are different as SPRINT required a minimum degree of existing vascular risk while WRAP does not, possibly accounting for differences seen in baseline WMHV.

TARGET PRODUCT PROFILE AND DESIGN PATH TOWARD Dyr533: A SMALL MOLECULE TOWARD AD AND IND-ENABLING STUDIES. Rokey S, Foley C, Shaw Y, Bartholomew SK, Winslow W, Dunckley T, Velazquez R, Hulme C. University of Arizona; Arizona State University; Illuminos Therapeutics, LLC; Arizona Alzheimer's Consortium.

Background: Targeting Alzheimer's disease (AD) pathology at single components is not likely to be feasible, and a successful therapeutic strategy may require pleiotropic interventions. Dyrk1a is an emerging target for the treatment of neurodegenerative diseases, attractive for its functional activity on multiple pathways implicated in AD and neuronal function. For example, Dyrk1a phosphorylates Tau, APP and presenilin 1 and as such ties into both amyloid aggregate and NFT production. Moreover, Dyrk1a promotes signal transduction in the JAK/Stat pathway, a well-known mediator of neuroinflammation (Fig. 1). The Dyrk1a gene is also located within the Down Syndrome (DS) critical region on chromosome 21 and overexpression is a significant contributor to the underlying neurodevelopmental and AD-related abnormalities associated with DS. Transgenic animals overexpressing Dyrk1a also show marked cognitive deficits and impairment in hippocampal dependent memory tasks. This poster details the small molecule discovery path over 10 years from Dyrk1a hit, to lead (POC with Dyr219) to Dyr533, now ready to commence IND-enabling studies.

Methods: Herein, we detail synthesis, small molecule design concepts, mechanism-based safety studies (Safety Pharmacology Panel 87, genotoxicity, time dependent and independent CYP inhibition, hERG assay), ADME surrogate data (PAMPA, MDCK, Qik Prop Calculations, microsomal and hepatocyte stability across five species), PK data (two species), pharmaceuticals (aq. solubility, pKa, log P) and kinome selectivity data (KinomeScan™) of Dyr533. Dyrk1a degradation studies.

Results: Results presented, combined with efficacy studies presented in a sister poster, establish Dyr533 as ready to commence IND-enabling studies.

Conclusions: Dyrk1a is a pre-clinically validated target, with a dual small molecule inhibitor and degrader possessing pre-requisite properties to move into the IND-enabling phase.

TDP-43 INDUCED TRANSCRIPTIONAL CHANGES IN ALZHEIMER'S DISEASE. Pevey R, Moore S, Antone J, Alsop E, Hall W, Preller K, Mufson E, van Keuren-Jenson K, Sattler R. Barrow Neurological Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: TDP-43 is an RNA binding protein that is a pathological hallmark of multiple neurodegenerative diseases including Alzheimer's disease (AD) and related dementias. Remarkably, wild-type TDP-43 protein associates with pathological inclusions in multiple dementias regardless of etiology. The frequency of observed TDP-43 pathology varies between 30-57% in AD and 45% in frontotemporal dementia (FTD) and a common feature is mislocalization of TDP-43 from the nucleus to the cytoplasm where it is associated with aggregates of varied shapes. The normal function of TDP-43 has been linked to multiple steps in RNA processing including transcription, splicing, RNA transport, stability, localization, and translation. TDP-43 also has autoregulatory functions where the protein inhibits its own transcription. Most studies aimed at understanding TDP-43 pathology have been performed in the context of ALS and FTD, while little is known about the molecular mechanisms and consequences of TDP-43 pathology in AD. We hypothesize that TDP-43 dependent alterations in gene expression, in neurons with TDP-43 pathology are responsible for neuronal dysfunction and degeneration in AD and related dementias.

Methods: We will use FACS to enrich RNA from NeuN+/TDP-43+; NeuN+/TDP-43- neuronal nuclei for RNAseq as described in Lui et al. (2019). Fusiform gyrus (500 mg) will be Dounce homogenized, nuclei isolated by gentle centrifugation in successive washes of Nuclei EZ lysis buffer and fluorescently stained for NeuN and TDP-43. Stained nuclei will be sorted on NeuN and TDP-43 fluorescence. Additionally, Laser capture microdissection (LCM) will be used on intact post mortem tissue to isolate neurons with cytoplasmic TDP-43 inclusions. A rapid immunohistochemistry (IHC) staining method as described in Mastroeni et al. (2017), will be performed on 20 μ m-thick fresh frozen tissue sections using sTDP-43 or pTDP-43 specific antibodies followed by a methyl green pyronin counterstain to identify cellular morphology. Approximately 300 individual labeled cells will be microaspirated and processed for downstream RNA-Seq. We will also characterize cytoplasmic TDP-43 inclusions and co-localization with stress granule markers. induce cytoplasmic TDP-43 mislocalization in stably expressed inducible TDP-43 overexpressing SH-SY5Y cells as well as endogenously labeled eGFP-TDP-43 SH-SY5Y cells using established stress paradigms: sodium arsenite, or sorbitol. Nucleocytoplasmic (N/C) ratios are measured as nuclear depletion and/or cytoplasmic TDP-43 accumulation, an established assay as well as a western blot based nuclear cytoplasmic fractionation protein assay.

Results: We have optimized nuclei isolation and FACS parameters as well as LCM staining. The stress induced TDP-43 mislocalization paradigm in mammalian cell lines has been validated. IHC staining and confocal image quantification Subcellular fractionation. Validated stress induced TDP-43 mislocalization in patient derived iPSC neurons.

Conclusions: We optimized nuclei isolation methods for future qPCR validation and RNA sequencing analyses. We have received human post-mortem Alzheimer's disease patient tissue with confirmed TDP-43 proteinopathy (AD-TDP+) and will isolate TDP-43 normal and aberrant neurons using FACS. We have also obtained AD-TDP+ fibroblasts and iPSC lines which we will differentiate into cortical neurons for biochemical characterization and cellular stressing experiments. Future experiments also include determining whether cytoplasmic TDP-43 undergoes phosphorylation, forms ubiquitinated p62-positive inclusions and if it co-localizes with stress granules, all considered markers of pathological TDP-43 inclusions.

THE AUTOBIOGRAPHICAL INTERVIEW ADMINISTERED DURING THE 2020 SARS COV2/CORONAVIRUS PANDEMIC VIA ZOOM-BASED FORMAT. Hernandez DA, Griffith C, Deffner AM, Andrews-Hanna J, Grilli MD. University of Arizona; Arizona Alzheimer's Consortium.

Background: Decades of research have revealed that the Autobiographical Interview, a standardized method for evaluating episodic specificity for real-world events, reliably detects cognitive decline associated with Alzheimer's disease risk factors, including older age. To our knowledge, every published study of the Autobiographical Interview has been done in person. In-person research, however, was challenging at the start of the COVID-19 pandemic and introduced the need for virtual administered cognitive tests. The goal of the present study was to determine whether administering the Autobiographical Interview in a virtual format would replicate a reliable cognitive correlate of older age, namely reduced episodic specificity (i.e., specific details) of autobiographical event memories.

Methods: Cognitively unimpaired older adults (N=52 Age M = 69.6) were assessed and compared to a younger adult group (N=51 Age M= 35.2). During the Zoom-Based Autobiographical Interview, participants were asked to recall 5 memories from different periods throughout their lives. The Autobiographical Interview sessions were recorded and transcribed to be scored using the standard Autobiographical Interview protocol that assesses episodic specificity.

Results: Consistent with lab-based studies, older adults exhibited reduced episodic specificity relative to young adults. Specifically, while older adults generated significantly fewer "internal" (i.e., episodic) details relative to young adults ($p < 0.003$), they also generated significantly more "external" (i.e., semantic, language-based) details ($p < 0.010$).

Conclusions: The Autobiographical Interview, despite being developed in the laboratory, appears to be translatable to a virtual, Zoom-based format. These findings add promise to the possibility of using virtual cognitive testing during times when in-person research is less ideal because of location remoteness or public health concerns.

THE EMERGING ROLE OF ABERRANT TRANSFORMING GROWTH FACTOR- β (BETA) SIGNALING IN BRAIN PATHOPHYSIOLOGY. Curtin L, Curry T, Bromberg C, Krishna G, Currier Thomas T. University of Arizona College of Medicine Phoenix; Phoenix Children's Hospital; Midwestern University; Arizona Alzheimer's Consortium.

Background: Transforming Growth Factor- β (TGF- β) is a multifunctional cytokine expressed in virtually every cell type of the human body. It has various roles throughout the body and is heavily reliant on cellular and environmental context, with major roles in ECM turnover, inflammation, cell cycle regulation, among other roles. In the nervous system, TGF- β has been implicated in having both neuroprotective and pathological roles. TGF- β is expressed at a minimal level in the normal adult brain and has been observed to be upregulated in a variety of neurological insults including trauma, neurodegenerative diseases, and ischemic injury. As in peripheral tissues and systems, TGF- β has been observed to be expressed by both neurons and glia cells and is ubiquitously expressed in the nervous system in general. Recent investigations have begun to shed light on the ability of TGF- β to modulate neurotransmission with specific interest in the hippocampus. The present study investigates how local TGF- β application can modulate glutamatergic neurotransmission using anesthetized in vivo amperometric recordings.

Methods: Young adult (6M) male C57BL/6 mice (N=5) were utilized in the study to test the effects of local TGF- β application on glutamatergic neurotransmission, most notably assessing glutamate clearance times, uptake rate, and first order rate constant. In vivo amperometric recordings were accomplished utilizing ceramic-based microelectrode arrays (MEAs) equipped with 4 platinum recording surfaces. MEAs were coated with glutamate oxidase to catalyze the oxidative deamination of glutamate to yield H₂O₂, which was then electro-oxidized at a potential of +0.7 V to generate a current output which was converted to a glutamate concentration using an in vitro calibration factor specific to the MEA used determined the same day prior to experimentation. Other electroactive neurotransmitters were excluded via an mPD coating. Anesthetized animals (1.5g/kg, i.p.) underwent a craniectomy to allow access for MEA insertion into the lateral hippocampus (AP: -2.75, ML: \pm 3, DV: -1, -1.5, -2.2, -3, -4). MEAs were equipped with a double barrel micropipette attached to a Picospritzer to allow precise application of glutamate (100 μ M) and TGF- β (25ng/mL). In each layer of the lateral hippocampus, 4 amplitude matched glutamate peaks were obtained by local application of glutamate followed by application of 400nL (~10 pg TGF- β peptide) of TGF- β solution, after which 4 amplitude matched glutamate peaks were obtained to assess glutamate clearance parameters.

Results: Our data shows that TGF- β can modulate glutamatergic neurotransmission in 6M C57BL/6 mice in an acute timeframe. Glutamate clearance times were observed to increase, coinciding with a decrease in both glutamate uptake rate and first order rate constant. Experimentation was completed the week of August 1st and further analysis is underway to thoroughly assess data collected. It was also observed that local application of TGF- β yielded an evoked glutamate release. This surprising result is too being examined and analyzed further.

Conclusions: While statistical significance is yet to be fully realized across the cohort, the observations made implicate a role of TGF- β in modulating glutamatergic neurotransmission in the lateral hippocampus. This finding may be important in further understanding the role TGF- β may play in symptomology observed after neurological insult, especially insult yielding neuroinflammation in the brain and neurodegeneration, two instances that have been observed to coincide with an upregulation of TGF- β expression.

THE IMPACT OF CONTEXT ON MEMORY FOR SHORT STORIES AMONG OLDER AND YOUNGER ADULTS. Palmer JM, Guareña LA, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.

Background: On traditional pattern separation tasks, older adults perform worse than younger adults when identifying similar objects but perform equally well when recognizing repeated objects. When objects are superimposed on semantically related scenes, older adults are influenced by the context to a greater degree than younger adults, leading to errors when identifying similar objects. However, in everyday life, people rarely need to differentiate between two perceptually similar objects. Therefore, we developed a task using similar short stories to represent the similar events people may experience in daily life. Our goal was to investigate the influence of context, detail type, and age on memory performance.

Methods: Twenty-one older adults and 18 younger adults participated in a task where they listened to 20 short stories taking place in either a coffee shop or library, each paired with a unique picture (i.e., context). Participants were asked to imagine the story taking place within the picture. Approximately 20 minutes later, participants answered a yes/no question about a detail from a story superimposed on different contexts. The different context conditions were (1) the same picture from the original story, (2) a similar picture (i.e., a different library or coffee shop picture), (3) a dissimilar picture (i.e., a library picture instead of a coffee shop picture), or (4) a control using a Fourier-transform (FT) image without any spatial-context information. Questions either asked about an identical or similar detail from the story.

Results: Correct answers were analyzed using a 4x2x2 repeated measures ANOVA including context (same, similar, dissimilar, and FT), detail type (identical and similar), and age (younger and older adults). Overall, younger adults were more accurate than older adults, $F(1,37)=23.4$, $p<0.001$. However, surprisingly, the context and detail-type made no difference in accuracy, (F 's <1.1) A similar model was used to analyze reaction times. Younger adults were faster than older adults, $F(1,37)=23.4$, $p<0.001$. Participants of both ages were faster at correctly responding to the identical detail than the similar detail, $F(1,114)=62.87$, $p<0.001$. Context also impacted reaction time, $F(3,114)=7.97$, $p<0.001$. All participants were faster while viewing same and similar contexts compared to both the dissimilar and FT contexts ($t(39)$'s >2.20 , p 's <0.05).

Conclusions: We did not find the kinds of age-related effects normally observed on traditional pattern separation tasks. Although younger adults performed better overall, older adults were not any worse when responding to a similar detail compared to an identical detail, which is inconsistent with performance on pattern separation tasks where older adults perform worse when identifying similar objects compared to younger adults. Additionally, older and younger adults were influenced by context in the same way. Previous studies from our laboratory demonstrated that older adults are biased toward the context when recognizing similar objects, but the context in this paradigm did not differentially influence accuracy for either older or younger adults. Potentially, this task relies on more semantic similarity rather than the perceptual similarity of objects. Semantic similarity from the short stories may incorporate more information to better orthogonalize similar memories, rendering retrieval less susceptible to interference.

THE IMPACT OF COVID-19 RESPIRATORY SYMPTOMS & LEVELS OF NFL AMONG OLDER ADULTS ON COGNITIVE PERFORMANCE. Galdamez-Avila A, Palmer JM, Lee Ryan L. University of Arizona; Arizona Alzheimer's Consortium.

Background: The SARS-CoV-2 virus disproportionately affects older adults 65 years and older, where age is a strong risk factor for more severe symptoms, more frequent hospitalization, and increased mortality. Acute respiratory distress syndrome (ARDS) is a common severe symptom in individuals with COVID-19. Older adults with ARDS may experience a high prevalence of cognitive impairment in areas of executive functioning and memory that interfere with daily life. Additionally, recent reports suggest that neurofilament light protein (NfL), a known biomarker of axonal injury in neurodegenerative diseases, stroke, brain trauma, and cardiovascular disease, may be sensitive to neuronal damage in severe COVID-19 patients. We investigated how the severity of respiratory symptoms in older adults who have recovered from COVID-19 and levels of circulating NfL impacted cognitive performance on two hippocampally-mediated tasks.

Methods: Participants were divided into groups based on a self-report measure of respiratory symptom severity at the time of infection. Group 1 included COVID-19 positive individuals without respiratory symptoms, Group 2 included COVID-19 positive individuals with mild respiratory symptoms (e.g., labored breathing/shortness of breath), and Group 3 included hospitalized COVID-19 patients with ARDS. Finally, Group 4 included COVID-19 negative controls. Participants were tested on a thorough battery of cognitive tests, which included the Mnemonic Similarity Task (MST, i.e., pattern separation) and the Face-Name Associative Memory Exam (FNAME). Both the MST and the FNAME are tasks known to rely on the hippocampus. For the MST, participants are first shown common objects on a white background and identify if the object is found indoors or outdoors. Participants are then given a surprise memory test where they identify identical and perceptually similar objects. For FNAME, twelve different faces are shown one at a time, each with a different name and occupation. Participants have two learning trials followed by a short and long delay with a recognition trial. Blood was also collected to measure levels of circulating NfL.

Results: Data collection is still ongoing, but preliminary analysis are described below. The total correct names recalled on the FNAME between the four COVID-19 groups was analyzed using a one-way ANOVA. A significant effect of group, $F(3,39)=4.55$, $p<0.01$, and post-hoc Tukey's HSD Test for multiple comparisons indicated that the controls performed better than the hospitalized group, $p<0.01$, and controls performed marginally better than the COVID-19 group with no respiratory symptoms, $p=0.06$. The primary outcome measure from the MST was the proportion of correct identification of similar objects after accounting for false alarms. This proportion was correlated with levels of NfL (pg/mL) and suggest that higher levels of NfL may be associated with fewer correct identifications of similar objects.

Conclusions: The most severe cases of COVID-19 resulted in poorer memory performance. However, even mild cases appeared to perform worse than individuals who have not had COVID-19. Importantly, a lot of variability within these groups exist, suggesting that other factors beyond respiratory symptoms may account for memory performance. Additionally, higher levels of NfL may be associated with poorer pattern separation performance.

THE LONG AND WINDING ROAD: DO DIFFERENT PATHWAYS TO HYSTERECTOMY LEAD TO THE SAME COGNITIVE DESTINATION? Pastor J, Bernaud V, Bandin E, Dyer C, Mayer L, Hanson T, Ruhland A, Bimonte-Nelson HA. Arizona State University; FYXX Foundation; Arizona Alzheimer's Consortium.

Background: Hysterectomy is the second most common gynecological procedure in women, and it often takes place before the onset of natural menopause which is associated with ovarian follicular depletion. Preclinical work in rats has shown that hysterectomy and experimentally-induced ovarian follicular depletion each individually impact cognition. There have been limited studies evaluating whether hysterectomy is impacted by prior follicular depletion; that is, addressing whether the combination of hysterectomy and follicular depletion initiate a unique series of behavioral and physiological effects.

Methods: In order to evaluate our interactive question, two rodent models of menopause were combined to create a 2x2 experimental design assessing two independent variables: Follicular Depletion (e.g., experimentally-induced transitional menopause via 4-vinylcyclohexene diepoxide, VCD, or Vehicle) and Surgery (Hysterectomy, Hyst, or Sham). Thus, the experimental groups were: Vehicle-Sham, Vehicle-Hyst, VCD-Sham, and VCD-Hyst. Vehicle or VCD treatment was administered. Once the timeframe for follicular depletion occurred, subjects underwent sham or hysterectomy surgery. A battery of behavioral tests was then performed; for this poster, we will focus on outcomes for the complex spatial working and reference memory task, the water radial-arm maze, including a delayed memory retention protocol. Other peripheral markers of hormone status and health were also evaluated, including ovary weights, body weights, and uterine weights.

Results: Preliminary analyses indicate that hysterectomy, but only in combination with follicular depletion, impaired learning. In addition, rodents that underwent hysterectomy, with or without induced follicular depletion, showed impaired delayed memory retention. Interestingly, hysterectomy improved performance during the late acquisition phase of testing. These preliminary data suggest that some hysterectomy outcomes for cognition are influenced by whether prior follicular depletion has occurred; detailed behavioral analyses and changes in peripheral assessments will be discussed at the poster presentation.

Conclusions: Understanding how hysterectomy, combined with varied menopausal backgrounds, alters the brain and its function is vital for understanding the trajectory of neurocognitive changes across age in the female.

THE NOVEL DYR533 DYRK1A INHIBITOR REDUCES AD-LIKE PATHOGENIES IN THE 3XTG-AD MOUSE MODEL OF ALZHEIMER'S DISEASE. Bartholomew SK, 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: Currently, there are no effective therapies to ameliorate the pathological progression and associated cognitive deficits in Alzheimer's disease (AD), a rapidly progressing neurodegenerative disorder characterized by the formation of dense amyloid- β (A β) plaques and neurofibrillary tangles. The Dual-specificity tyrosine phosphorylation-regulated kinase-1a (DYRK1a) is known to phosphorylate both the tau and amyloid precursor protein (APP). Previous work has shown that DYRK1a is upregulated in postmortem brain tissue of patients with AD, and this increased activity has been associated with cognitive deficits. We have previously shown both reduced A β plaque deposition and decreased phosphorylated tau in the brains of the 3xTg-AD mouse model of AD when using a DYRK1a inhibitor termed DYR219.

Methods: Here, we utilized a more potent DYRK1a inhibitor, DYR533, which has a four-hour half-life, compared to the 15-minute half-life of DYR219, along with 100% bioavailability. Eight-month-old female 3xTg-AD and control mice were given daily intraperitoneal injections at either a 1.0 mg/kg, 2.5 mg/kg, 5.0 mg/kg or a vehicle control dosage for two months. At 10 months of age, mice were euthanized, and hippocampal and cortical tissue was harvested for neuropathological assessment.

Results: Enzyme-linked immunoassay (ELISA) showed that soluble cortical A β 42 levels were significantly reduced in the 1.0 mg/kg and 5.0 mg/kg 3xTg-AD DYR533 dosed groups compared to the vehicle group. Additionally, DYR533 decreased soluble and insoluble fractions of phosphorylated tau at serine 396 in hippocampal and cortical tissue of the 3xTg-AD mouse in a dose dependent manner. Notably, we found a reduction in phosphorylated tau at threonine 217, which was recently shown to be the earliest marker associated with AD progression.

Conclusions: Collectively, we demonstrate that the more potent, selective, and orally bioavailable DYRK1a inhibitor (DYR533) reduces A β pathology and tau phosphorylation, ultimately paving the way for further clinical development of this candidate AD therapeutic.

“THROUGH ALZHEIMER’S EYES”: A VIRTUAL PILOT INTERVENTION FOR CAREGIVERS OF PEOPLE WITH DEMENTIA. Gómez-Morales A, Carll P, Glinka A, Gonzalez-Pyles S, Perez S, Coon DW. Arizona State University; Arizona Alzheimer’s Consortium.

Background: The American population is rapidly aging, and it is widely known that Alzheimer's is a devastating disease affecting 6.5 million Americans aged 65 and older. As the disease progresses, these individuals require a devoted caregiver, most often a family member, who provides evolving complex care and experiences a variety of continuous stressors. Families are stretched beyond their capacity to care and often continue to juggle job responsibilities with complex caregiving duties impacting the caregiver's health and affecting the care recipient's quality of care and well-being. Information and communication technologies can provide an excellent opportunity for training caregivers remotely, regardless of their location and caregiving background, and help them manage their stressors. This pilot study explores the feasibility and acceptability of a Zoom-based intervention for caregivers of people with dementia that includes a Virtual Reality component.

Methods: "Through Alzheimer's Eyes" is a single-arm, pre-post-test pilot study consisting of 4 sessions of 90 minutes each delivered via Zoom. The intervention also includes a weekly in-session Virtual Reality experience in which the participant embodies the journey of Beatriz, an older Latina with Alzheimer's. In addition, the four sessions cover communication skills, management of challenging behavior and unhelpful thinking, the importance of self-care, and mindfulness—all of which are critical components to reducing stress in family caregivers. Outcomes are gathered via an online survey before and after the intervention and a post-intervention qualitative-focused individual interview: the surveys and interviews capture participant insights to evaluate feasibility, acceptability, satisfaction, and preliminary outcomes.

Results: Twenty (N=20) family caregivers participated and completed the study. Of these, 80% were female, 80% were spouses, and 80% lived in suburban areas. Their age ranged from 38 to 79 years (mean=64.1, SD=10.2). Care recipients were 75% male, and their ages ranged from 56 to 87 years (mean=74.7, SD=7.7). Participant responses to surveys and interviews indicated they benefited from the intervention through improved communication with their loved ones (95%) and others (75%), care preparedness (90%), confidence in providing care for their loved one (95%), and emotional wellbeing (85%). Regarding the satisfaction of the program, participants found the intervention useful, technologically easy, and enjoyable. Participants stated that it was easy to connect to the sessions via Zoom and use the VR headset adapted for mobile phones. The sessions helped caregivers understand better care recipient behavioral challenges through this “eye-opening” experience. Also, caregivers expressed interest in having longer Virtual Reality modules and a wider variety of scenarios. They would recommend this innovative workshop to other caregivers and suggested the Virtual Reality experience be provided to other family members to help them understand Alzheimer’s disease and related dementias.

Conclusions: “Through Alzheimer’s Eyes” is a new approach to interventions that combines technological innovation and skill-building strategies and leverages existing technology to help caregivers manage their stress regardless of their location and personal situation. Feasibility outcomes and qualitative analyses suggest the need for a larger trial with a longer VR experience.

TRANSFER LEARNING BASED DEEP ENCODER DECODER NETWORK FOR AMYLOID PET HARMONIZATION WITH SMALL DATASETS. Shah J, Chen K, Reiman EM, Li B, Wu T, Su Y. Arizona State University; Mayo Clinic Arizona; Banner Alzheimer's Institute; University of Arizona; Arizona Alzheimer's Consortium.

Background: The existence of multiple amyloid tracers with varied characteristics poses a significant challenge to standardized interpretation and quantification of amyloid PET data. We previously demonstrated that a deep learning model using a residual inception encoder-decoder network (RIED-Net) architecture improved harmonization of florbetapir (FBP) and PiB PET. However, scarcity of head-to-head comparison datasets of other amyloid PET tracer may limit the ability to generalize this approach to the other amyloid PET tracers. In this research, we investigate the performance of RIED-Net model trained on smaller datasets and explore transfer learning (TL) approaches which can leverage multiple different datasets and address the data scarcity issue.

Methods: We previously trained our RIED-Net model using PiB-FBP data from Open Access Series of Imaging Studies (OASIS) (N=92) and tested the performance in the independent Global Alzheimer's Association Interactive Network (GAAIN) (N=46) dataset. We now use the same procedure to train the RIED-Net model using the smaller GAAIN dataset and evaluate the model performance. We then examine the feasibility of a TL approach by comparing the model performance between RIED-Net model directly trained on the PiB-florbetaben (FBB) from GAAIN (N=35) and the TL approach in which we started with the optimal RIED-Net model for PiB-FBP data and fine-tuned the network parameters using the GAAIN PiB- FBB data. A cross-validation (CV) approach was used to evaluate model performance based on difference before and after harmonization in terms of correlation between mean cortical SUVR (mcSUVR) measurements from different tracers.

Results: RIED-Net model trained using the smaller GAAIN PiB-FBP data improved the agreement of mcSUVR measurements as measured by Pearson correlation from $r=0.93$ to $r=0.96$ ($p<0.01$) on test-set. For PiB-FBB harmonization, the TL approach provided numerically better agreement in mcSUVR from $r=0.96$ (direct train) to $r=0.97$ (with TL), demonstrating the potential benefits of applying TL based technique to address the issue of smaller sample size.

Conclusions: We demonstrate our RIED-Net model can achieve improved harmonization even when trained on a relatively small training set. We also demonstrate the potential of transferring knowledge learned from one tracer pairs to improve the harmonization model of other related tracer pairs.

TRANSLATION OF POST MORTEM MRI METHODS TO CLINICAL SCANNER PROTOCOLS FOR THE DETECTION OF MICROSTRUCTURAL PATHOLOGY IN ALZHEIMER'S DISEASE.

Comrie CJ, Chen NK, Johnson K, Hutchinson EB. University of Arizona; Arizona Alzheimer's Consortium.

Background: The identification of sensitive and specific brain imaging markers is a primary goal for neuroimaging in Alzheimer's disease (AD). While advanced microstructural MRI approaches – especially non-Gaussian diffusion and multi-compartment relaxometry MRI methods – are conceptually appealing to report and differentiate cellular and macromolecular pathology, they have not yet been overly successful. Previously, we identified promising microstructural MRI markers in post-mortem tissue utilizing DTI, MAP-MRI, BPF, and MWF at high resolution and image quality. The objective of this study was to translate post-mortem techniques to in-vivo clinically feasible MRI protocols on a human MRI scanner.

Methods: Healthy volunteers were recruited both for MR battery development (n=9), and test-retest reliability (n=6) of acquisition where volunteers each participated for two separate scan sessions to compare within and between subject variability of microstructural MRI maps. Scans were developed on a 3T Skyra Siemens Scanner in the Translational Bioimaging Resources (TBIR) at the University of Arizona. A reduced field of view (FOV) strategy was used for all scans in which slices were strategically prescribed according to the main axis of the hippocampus. Efficient and high quality diffusion MRI scans were the focus of development including 4PAT acceleration and 4-way phase acquisition (H-F, F-H, L-R, R-L) using bvalues 250s/mm³ (12 directions), 500s/mm³ (46 directions), and 1000s/mm³ (64 directions). Images had a voxel size of 1x1x1.5 mm. A high angular resolution diffusion imaging (HARDI) shell was also acquired with 2-way phase acquisition (L-R, R-L) with b=3000s/mm³ and 64 directions and voxel size of 2x2x3 mm. Additionally, T1 maps were acquired utilizing 2 flip angles and multi-echo T2 scans to support MWF mapping were collected utilizing a radial acquisition. Diffusion data was corrected for motion (DIFFPREP) and distortion (DRBUDDI) artifacts using TORTOISE 3.1.4 while also recombining all phase direction groupings and up-sampling the HARDI shell during the DRBUDDI corrections. All diffusion data was concatenated before mapping diffusion tensor imaging (DTI), mean apparent propagator (MAP-MRI), and neurite orientation dispersion density imaging (NODDI). Currently MAP-MRI and NODDI have been achieved for the development data, but are still being processed for reproducibility dataset.

Results: Desired quality and resolution were achieved for DTI, MAP-MRI, and NODDI maps using the reduced FOV strategy for high-resolution hippocampal imaging. Preliminary results from two-way random Intraclass Correlation Coefficient (ICC2) analysis for whole brain fractional anisotropy (FA), produced an ICC value of 0.768 corresponding to “good” reliability.

Conclusions: Correction of geometric distortions and improvement in DWI image quality (i.e. SNR) were successful using 4-way phase correction and image combination. Additionally, MAP-MRI and NODDI modeling were both successful using the multi-shell and multi-resolution strategies developed in this study. While basic relaxometry techniques were successful, it is the goal of ongoing work to develop successful models for MWF with these scans. Preliminary reproducibility data of whole brain FA showed a low intraclass variability for participants with a ICC2 in the accepted “good” range (between 0.75 and 0.90) providing promising results on methods reliability. The desired image quality to visualize the hippocampus was achieved. Next steps include completing MAP-MRI, NODDI, T2, and MWF mapping techniques on the reproducibility dataset. Voxelwise analysis and ICC2 will be conducted on all maps after completion to evaluate the reproducibility of the developed methods.

TRANSLATIONAL POTENTIAL OF JAX HUMANIZED APOE MICE: PERIPHERAL INTERFERON GAMMA INDUCES SYSTEMIC IMMUNO-METABOLIC DYSFUNCTION. Van Rossum H, Delatorre N, Mishra A, Bhattra A, Raikes A, Rodgers K, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.

Background: Inflammation is a well-documented feature of Alzheimer's disease (AD) in human brain. Previous findings from our group demonstrated upregulated immune transcripts in the AD brain as well as sex differences in immune transcript levels during pre-clinical midlife aging. Using our humanized APOE mouse model, we identified elevated immune transcripts in the female brain including interferon signaling genes, CD3, CD4, and MHCII. We hypothesized that activation via increased interferon gamma (IFN- γ) during endocrine aging may disrupt the immune-metabolic balance in the brain and therefore advance changes in grey and white matter. With this study, we test the hypothesis that increased levels of peripheral IFN- γ induces genotype dependent immuno-metabolic changes in the JAX humanized APOE (hAPOE) mouse model.

Methods: To determine the role of IFN- γ in female midlife aging and AD risk, pre-menopausal and peri-menopausal hAPOE mice were intraperitoneally treated with recombinant IFN- γ for 9 days. Immunophenotyping using multi-color flow cytometry was conducted microglial reactivity, phagocytosis, neutral lipid content, oxidative stress, and the presence of lymphocytes were determined. Structural and diffusion weighted analysis using MRI was conducted to evaluate grey and white matter structural integrity in the brain. ELISA assays were conducted to assess the presence of beta amyloid 40 and 42 and levels of pro-inflammatory cytokines.

Results: IFN- γ treated animals exhibited upregulation of markers that perpetuate neuroinflammation and white matter catabolism including MHCII, CD8, pHrodo, and BODIPY. Peripheral immune effects were genotype dependent while immune signaling in brain largely exhibited treatment-dependent effects. Fasting blood glucose levels were significantly increased by IFN- γ consistent with an accelerated aging profile. Diffusion metrics including mean and radial kurtosis in addition to mean, axial, and radial diffusivity were greater in IFN-treated animals.

Conclusions: Peripheral increase of interferon gamma signaling during female endocrine aging in hAPOE mice induced 1) dysfunction of metabolic systems and neuroinflammatory response and 2) decreases in white and grey matter microstructural integrity throughout the brain. These outcomes support the investigation of therapeutic strategies targeting interferon signaling pathways at the earliest stages of midlife aging to reduce risk of AD or delay AD onset.

TRANSLATIONAL POTENTIAL OF JAX HUMANIZED-APOE MICE: SEX DIFFERENCES IN BIOENERGETIC FUNCTION IN BRAIN. Cortes-Flores H, Altemus J, Wiegand JP, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.

Background: The preclinical phase of late onset Alzheimer's disease (LOAD), known as the preclinical phase, can start 10 to 20 years prior to onset of clinical symptoms. Hypometabolism and impaired mitochondrial bioenergetics can emerge during prodromal phase as early indicators of AD risk. APOE ϵ 4, the greatest genetic risk factor for LOAD, is well documented to induce lipid metabolic dysregulation. We therefore sought to determine the impact of APOE ϵ 4. The following study analyzed body composition and mitochondrial functions to elucidate how the presence of APOE ϵ 4 in a mouse model contributes to bioenergetic changes, and whether they affect females and males equally.

Methods: 18mo old transgenic mouse models (JAX #029018 and #027894) carrying humanized APOE alleles (hAPOE3/3, hAPOE3/4 or hAPOE4/4) were assessed for fat and lean mass content via EchoMRI. A week later, fasting blood glucose levels were assessed prior to sacrifice, and brain tissues were collected to determine mitochondria function by Complex I and IV activity.

Results: Body composition analyses indicated that hAPOE ϵ 4 males had significantly lower fat percentage than male APOE ϵ 3 mice. Females, irrespective of APOE genotype, exhibited significantly lower lean weight relative to males. No sex or APOE genotype difference was detected in fasting blood glucose plasma levels nor in mitochondrial Complex I activity. In contrast, mitochondrial Complex IV activity was significantly lower in females relative to males. Lastly, Complex IV activity was lower in mice exhibiting dominance aggressive behavior, specifically barbering, irrespective of sex or genotype.

Conclusions: APOE mice resembling a human population of approximately 60 years of age displayed a sex difference in body composition parameters, where total and lean weight was higher in males than females. Sex differences also emerged in bioenergetic function, with females exhibiting lower mitochondria Complex IV activity relative than males. Sex differences are consistent with human data, whereas no genotype differences were observed and thus may influence the translational potential of the humanized APOE mouse model in LOAD research. However, the translational potential might be greater when linked with phenotypic characteristics.

This work was supported by NIA grant R01AG057931, and RF1AG059093

TRANSLATIONAL POTENTIAL OF THE JAX HUMANIZED APOE AD MOUSE MODEL: METABOLISM AND BODY IN MICE EQUIVALENT TO 60-70YR OLD HUMAN. Bhattra A, McLean W, Raikes A, Wiegand JP, Skopp S, Howison C, Galons JP, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.

Background: Apolipoprotein (APOE) is the strongest genetic risk factor for the development of late-onset Alzheimer's disease (LOAD). Clinically, LOAD exhibits strong sex effects with females being twice at the risk of developing AD than males. Models exhibiting strong AD etiology are used in preclinical settings, however lack of translatability necessitates model development with a reverse translational approach. This study explores metabolic hallmarks of LOAD assessing the clinical translatability of the JAX humanized APOE (hAPOE) mouse model.

Methods: hAPOE mice (M/F, n = 65, mean age = 23.35 +/- 0.90 months) with e3/3, e3/4 or e4/4 genotype underwent a metabolic and body composition screening assay including fasting blood glucose (FBG) and ketone (FKB) measurement, EchoMRI, and 18F-FDG-PET brain imaging, prior to being sacrificed. Blood plasma was analyzed for triglyceride levels. Cerebral FDG-PET standardized uptake values were normalized to cerebellum. All data were analyzed with genotype x sex analysis of variance. $P \leq 0.05$ was considered statistically significant and post-hoc pairwise analyses were conducted for interaction effects with $p \leq 0.1$ (FKB, adipose index) for future study planning.

Results: Females had significantly lower lean mass ($p < 0.0001$) and FBG ($p=0.05$), with a trend toward lower glucose uptake on FDG-PET compared to males ($p=0.072$). Post-hoc interaction analyses of FKB (interaction $p=0.105$) demonstrated lower ketone body levels in male e4/4s compared to female e4/4s (uncorrected $p=0.0685$) and male e3/4s ($p=0.034$). Post-hoc interaction analyses of adipose index (interaction $p=0.093$) demonstrated greater adiposity in female e4/4s compared to male e4/4s (uncorrected $p=0.005$) and female e3/3s (uncorrected $p=0.035$). No main effects of genotype in any analyses conducted.

Conclusions: In a mouse cohort at a comparative human age of ~ 70 years, lower lean mass, fasting blood glucose, and glucose uptake in the brain for female mice indicates ongoing bioenergetic deficits and is corroborated by observations within clinical populations. Greater adiposity in female e4/4s suggests that bioenergetic needs are not being met through fat reserves in this group.

TREATMENT FOR PHONOLOGICAL TEXT AGRAPHIA IN LOGOPENIC VARIANT PRIMARY PROGRESSIVE APHASIA: A HETEROGENEOUS CASE SERIES. Nickels KV, Beeson P, Rising K, Jebahi F, Frazie NJ, Kiehar A. University of Arizona; Arizona Alzheimer's Consortium.

Background: Individuals with the logopenic variant of primary progressive aphasia (lvPPA) experience deficits in written language comparable to those observed in individuals with left perisylvian damage after stroke. Specifically, it has been documented that in individuals with stroke aphasia, weak phonological skills fail to support the use of function words and grammatical markers in text-level writing (phonological text agraphia), and that directed phonological treatment can improve grammatical accuracy. Previous studies have not yet documented the nature of text-level writing deficits in lvPPA nor explored the value of phonological treatment in remediating written language. Additionally, limited information is available regarding the contribution of transcranial direct stimulation (tDCS) as an adjuvant to phonological intervention.

Methods: We investigated the therapeutic value of phonological treatment, coupled with tDCS, in three participants with lvPPA (LV12, LV19, LV21). On comprehensive baseline assessment, all three participants demonstrated impairment on tasks that required phonological awareness and manipulation (e.g., sound blending – “Put these sounds together: ‘c’-‘a’-‘t’”; deletion – “Say ‘cat.’ Now take away ‘c’”; and replacement – “Say ‘cat.’ Now change the ‘c’ to ‘f’”). Text-level writing was marked by the omission of function words resulting in grammatically incomplete sentences. Spelling errors and letter-selection errors were also present. Phonological treatment targeted blending, deletion, and replacement of words and nonwords. Treatment sessions took place every weekday for two weeks, followed by a two-month rest, and then a second two-week period of treatment. Participants were randomized to receive an anodal tDCS condition during one of the treatment phases, and a sham condition during another. Generalization of treatment effects was measured on written narratives in response to the Western Aphasia Battery picnic scene.

Results: Following treatment, all three participants demonstrated improvements in phonological manipulation skills (LV12 – 73% to 95%; LV19 – 56% to 72%; LV21 – 86% to 88%). Striking improvements were observed in the production of grammatically complete sentences (LV12 – 0% to 100%; LV19 – 80% to 100%; LV21 – 50% to 100%), with the number of functors increasing from 44% to 57% for the group. Overall accuracy, which measures spelling accuracy relative to the number of words produced, improved from 64% to 89% at the group level. Finally, the amount of meaningful content produced increased from 83% to 97% for the group.

Conclusions: There is urgency to develop robust protocols for individuals living with progressive language loss, and these data present compelling evidence regarding the approach that targets weakened phonological skills in lvPPA. All three participants demonstrated improvements in phonology that generalized to improvements in text-level writing, a functional communication skill important in everyday life.

USING FREE-WATER DIFFUSION TENSOR IMAGING TO IDENTIFY MICROSTRUCTURAL DIFFERENCES IN A PRECLINICAL MODEL OF ALZHEIMER'S DISEASE. Nelson MR, Bergamino M, Numani A, Scarpelli M, Healey D, Fuentes A, Turner G, Oddo S, Stokes AM. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium

Background: Alzheimer's disease (AD) is the most common form of dementia. Preclinical mouse models of AD have been developed to recapitulate phenotypical AD features, including amyloid and tau pathology, along with functional changes. In vivo assessments of AD can be performed using imaging biomarkers, including through magnetic resonance imaging (MRI). Different MRI approaches can be used to detect changes associated with AD, in both preclinical models and human studies. For instance, diffusion tensor imaging (DTI) relies on the movement of water molecules to assess white matter microstructure. In this study, free-water (FW) diffusion tensor imaging (FW-DTI) was used to remove the influence of extracellular FW and to study the microstructural differences in white matter between 3xTg-AD and wildtype (WT) mice. Additionally, the imaging results were compared with the histological analyses of amyloid and tau protein in regions across the brain.

Methods: This study included 12 WT and 11 3xTg-AD mice (all female). MRI data were acquired at 7 T (Bruker Biospec). Diffusion was acquired with 30 directions ($b=700$ s/mm²) and 5 b0 images. Following imaging, perfusion-fixation was performed, and brains were extracted. DTI pre-processing was performed by FSL (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki>) and included brain extraction, alignment, eddy current correction, and DTI fitting (for standard fractional anisotropy, FA). FW-corrected FA (FW-FA) and FW index were computed by an in-house MATLAB script. Microstructural white matter differences were assessed both on a voxel-wise and a region-of-interest (ROI) level. A two-sample t-test was conducted by an in-house R script to compare FW-DTI metrics in 3xTg-AD and WT mice for both the voxel-wise and ROI analyses. Specific brain regions were defined by an automated multi-atlas segmentation approach. Statistical significance was considered at $p < 0.05$ after correction for multiple comparisons (false-discovery rate, FDR). Histology was performed on the fixed AD and WT brains to visualize phosphorylated tau protein (AT8 staining) and both diffuse (6e10 staining) and dense (thioflavin staining) amyloid-beta plaques. Microscopy images were imported to Qupath (V0.3.0) for analysis.

Results: On a voxel-wise level, clusters of lower FA and FW-FA values and higher FW index were observed in the thalamus, hippocampus, and fimbria of 3xTg-AD mice, relative to WT mice. These findings were similarly confirmed by ROI analysis. Higher FA and FW-FA values and lower FW index were also observed in the corpus callosum for the 3xTg-AD mice, which could be attributed to a loss of crossing fibers. As DTI is unable to distinguish between crossing fibers in the brain, more advanced models may be assessed in future studies. On histopathology, the 3xTg-AD mice were associated with higher AT8 and 6e10 in all regions, compared to WT mice. Significant increases in thioflavin were also found in the amygdala, corpus callosum, and hippocampus in the 3xTg-AD mice.

Conclusions: Using both voxel-wise and ROI analysis, microstructural differences were observed in the white matter between the AD and WT groups. AD mice had lower FA and FW-FA values and higher FW index in the fimbria, hippocampus, and thalamus, indicative of neurodegeneration in these brain regions of the transgenic mice. These regions were also associated with high levels of AD pathology (i.e., tau and amyloid). Future work will assess complementary gray matter atrophy in these cohorts. The current findings suggest that microstructural dysfunction in AD, as assessed via DTI, may be associated with amyloid and tau pathology, as assessed via histology methods.

VALIDATION OF A CLINICAL SCALE FOR DEFINING RBD SEVERITY IN PARTICIPANTS OF THE NORTH AMERICAN PRODRIMAL SYNUCLEINOPATHY (NAPS) CONSORTIUM.

Busicescu A, Choudhury P, Lee-Iannotti JK, Rangan P, Shprecher D, Fantini ML, Lim M, Elliott J, Avidan A, Huddleston D, Bliwise D, Howell M, Schenck C, Criswell S, During E, Mignot E, McLeland J, Pelletier A, Gagnon J, Forsberg L, Fields J, St. Louis E, Videnovic A, Ju Y, Boeve B, Postuma R. University of Arizona College of Medicine-Phoenix; Banner Sun Health Research Institute; Banner University Medical Center; Le Centre Hospitalier Universitaire; Oregon Health & Science University; Ohio Health; David Geffen School of Medicine at UCLA; Emory University; University of Minnesota; Minnesota Regional Sleep Disorders Center; Washington University; Stanford University; Stanford Center for Sleep Sciences and Medicine; Montreal General Hospital; Center for Advanced Research in Sleep Medicine; Mayo Clinic; MGH Neurological Clinical Research Institute

Background: RBD is a prodromal marker of α -synucleinopathies with no standardized tool for assessing severity in clinical or research practice. This study assessed the validity of the REM Sleep Behavior Disorder (RBD) symptom severity scale (RBDSSS) developed by the International RBD Study Group and its correlation to the clinical global impression of severity (CGI-S) in a cohort of participants enrolled in the North American Prodromal Synucleinopathy (NAPS) study.

Methods: Participants and their bedpartners in the NAPS cohort filled out an 8-item questionnaire, developed by the International RBD Study Group, assessing frequency and severity of dreams, vocalizations, movements, and injuries associated with RBD, with higher scores indicating more severe symptoms. The CGI-S is a 7-point scale ranging from normal (1) to most severely ill (7) and was completed based on an independent interview with the participant \pm their bedpartners. Total scores for participant (RBDSSS-PT) and bed partner (RBDSSS-BP) questionnaires were derived by multiplying assigned point values for frequency and severity (for each question) and summing them with total possible scores of 54 and 38, respectively.

Results: The median (interquartile range) for RBDSSS-PT, RBDSSS-BP and CGI-S was 10 (4-18), 8 (4-15) and 3 (3-4), respectively. Spearman's rank correlation coefficients (rs) were as follows: RBDSSS-PT vs. RBDSSS-BP, $rs=0.561$; RBDSSS-PT vs. CGI-S, $rs=0.556$; RBDSSS-BP vs. CGI-S, $rs=0.491$ ($p<0.0001$). RBDSSS-BP scores were significantly lower in women (6 vs. 9, $p=0.02$) while there were no differences in RBDSSS-PT scores between sex. (8 vs. 10.5, $p=0.615$). Item response analysis showed a high discriminatory value (range 1.40 – 2.12) for RBDSSS-PT and RBDSSS-BP (1.29-3.47).

Conclusions: The RBDSSS is a valid tool, with adequate psychometric properties to quantify RBD severity in isolated RBD. There is good concordance between participant and bed-partner questionnaires. Further studies are required to evaluate sex differences noted in the NAPS cohort.

VOLUMETRIC MRI ANALYSIS OF RODENT BRAINS AS A FUNCTION OF AGE AND COGNITION. Do L, Zempare MA, Bernstein AS, Bharadwaj PK, Carey N, Nguyen C, Alexander GE, Barnes CA, Trouard TP. University of Arizona; Arizona Alzheimer's Consortium.

Background: Animal models play an important role in preclinical and translational studies of the human brain. Magnetic Resonance Imaging (MRI) is a non-invasive technique that has the potential to provide reliable anatomical measures of the brain. Atlas-based tools for neuroinformatics can be utilized in studying age-dependent changes in brain anatomy associated with cognitive function in both animal models and in humans. Here we present results from a large cross-sectional study employing a rodent model of normative aging to investigate the correlates of healthy cognitive aging.

Methods: Initial analysis of MRI data utilized a rat brain template and associated atlas (Goerzen et al. 2020, Sci Rep 10:6952.) for comparison of rodent brain volumes both globally and regionally at 3 ages across the lifespan and at 3 levels of cognitive status within each age category. Male Fisher 344 rats (n=114) were acquired at young adult (6 months, n=48), middle aged (15 months, n= 38) and old adult (23 months, n= 28) ages. These rats underwent a battery of behavioral tasks over the course of 6 weeks resulting in each age group being sub-divided into 3 categorized subgroups of high, average, and low cognition using a corrected integrated pathlength score from the spatial version of the hippocampus-dependent Morris watermaze task. At the end of the 6 weeks, body weights were measured, and neurological MRI was carried out. Whole-brain T2-weighted images were collected at 150µm isotropic resolution. Images underwent brain extraction using a semi-automated process as well as bias correction due to non-uniform surface coil sensitivity. A Fischer 344 T2-weighted template image (60 µm isotropic voxels) and its labeled atlas (115 regions) were registered to each individual animal in the study using linear and non-linear registration.

Results: Two factor ANOVA models were used to assess differences in regional brain volumes, and total intracranial volumes across age and cognition groups. Significant main effect for age group was observed for total intracranial volume ($p < 0.0001$) and hippocampus volume ($p < 0.0001$). No significant interaction effects, or main effects of cognitive status were observed.

Conclusions: While there are many other ROIs to consider further, these initial findings indicate that intracranial volume and hippocampus volume are good predictors of the age of the animal, the intracranial volume is still increasing through middle age while the hippocampus continues to significantly increase into old age, however, the volume of the hippocampus is not related to cognitive status of the animals in these analyses.

VOLUMETRIC PREDICTORS OF EXECUTIVE FUNCTION IN COGNITIVELY UNIMPAIRED OLDER ADULTS. Andrew K, Malek-Ahmadi M. Arizona State University; Banner Alzheimer's Institute; University of Arizona College of Medicine-Phoenix; Arizona Alzheimer's Consortium.

Background: Studies of cognitive aging and cognitive impairment have focused primarily on cortical volume associations with episodic memory tests. However, there is increasing interest in executive function changes in aging and dementia and very few studies have investigated the associations between cortical volume measures and executive function. The aim of this study is to characterize a constellation of cortical regions associated with executive function using two different regression tree methods.

Methods: 374 cognitively unimpaired (CU) subjects from the Alzheimer's Disease Neuroimaging Initiative were used in the analysis. Freesurfer-based volumetric measures from the Desikan-Killiany atlas regions (35 ROIs) were used as independent variables while the ratio of Trails B to Trails A performance was used as the dependent variable. The ANOVA and Least Absolute Deviation (LAD) methods were each used to generate separate models.

Results: In a sample of 374 women made up 60% of the participants, while men made up 40% of the participants. The mean age was 73.71 ± 8.14 . The mean number of years of education was 16.78 ± 2.31 and the average MMSE score was 29.08 ± 1.12 . When comparing the ANOVA and LAD models, the following regions were used in both: superior frontal, pericalcarine, pars triangularis, lateral orbital frontal, and the anterior cingulate regions. The estimated Trails B/Trails A ratios for the ANOVA model ranged from 2.2 to 3.1 and 2.1 to 2.7 for the LAD model.

Conclusions: Two different regression tree approaches each found that volumetric measures of the superior frontal, pericalcarine, pars triangularis, lateral orbital frontal, and anterior cingulate regions were associated with executive function performance. Although further work is needed to refine and validate these models, this study demonstrates how the regression tree approach can be used to evaluate a large number of independent variables without relying on p-values to arrive at a proposed model.



**Arizona Alzheimer's Consortium
23rd Annual Scientific Conference**

Poster Presentation

Abstracts

A GENOME-WIDE SCREEN FOR HUMAN PROTEINS THAT AFFECT AMYLOID BETA PEPTIDE PRODUCTION BY GAMMA SECRETASE USING A YEAST GENETIC SYSTEM.

Adland E, Lewis KN, Sorenson K, Carpenter R, Chen C, Shumaker E, Solomon C, Pham C, Bae NS, Swanson MJ. Midwestern University; Arizona Alzheimer's Consortium.

Background: Accumulation of beta amyloid (A β) peptides in senile plaques is a hallmark of Alzheimer's disease (AD). A β peptides are formed by the cleavage of the amyloid precursor protein (APP) carboxyl-terminal fragment (C99) by γ -secretase. Normally, most A β peptides produced are soluble though some less soluble peptides are also made. When the ratio favors the more soluble form, the brain functions without AD-related pathology. Higher levels of insoluble peptides result in aggregation, senile plaque formation and ultimately AD. Mutations in APP or a protein in γ -secretase can lead to AD. How γ -secretase is normally controlled in cells is not understood. γ -secretase inhibitors were developed to reduce A β production, but the amelioration of AD by regulating γ -secretase is not straightforward. γ -secretase has numerous targets, and a general inhibitor may cause more harm than good. Small molecule inhibitors did not improve cognitive decline of patients, and in some cases worsened it. Several naturally occurring proteins that modulate γ -secretase activity (γ -secretase modulating protein or GSMP) have been identified. Each GSMP increases γ -secretase activity, and some affect multiple γ -secretase targets. Currently, there have been no screens to identify GSMPs that affect γ -secretase activity only on A β , and no screens have attempted to identify proteins that decrease γ -secretase activity.

Methods: We have reconstituted γ -secretase activity in yeast by expressing the four subunits of γ -secretase. Our target for γ -secretase activity is C99 fused to the yeast Gal4p transcriptional activator (C99-Gal4p). C99 will be embedded in the plasma membrane, sequestering Gal4p, and Gal4p target genes will not be expressed. When γ -secretase cleaves C99, Gal4p is released from the plasma membrane and enters the nucleus. γ -secretase activity is measured by determining Gal4p reporter gene expression. We have reporter genes that can be used to select yeast with increased and yeast with decreased γ -secretase activities. In addition to C99, we will use other γ -secretase target proteins to determine specificity of GSMPs. We will use known GSMPs to validate our system.

Results: To create cDNA libraries, we have isolated RNA from human neural cell lines under. We have developed a plasmid for the cDNA library. When γ -secretase is expressed from high-copy yeast plasmids, giving robust activity, we can screen for inhibitors. When γ -secretase is expressed from single-copy yeast plasmids, there is no detectable activity, allowing us to screen for activators. We are developing Notch1-Gal4p and CDH2-Gal4p targets to determine if effects we see are specific for C99.

Conclusions: We established a reconstituted γ -secretase system in yeast to determine effects of specific proteins on γ -secretase activity, which we will use to identify novel protein modulators of γ -secretase activity.

A HIGH-RESOLUTION 3D RECONSTRUCTION OF THE LOCUS COERULEUS IN AGED MACAQUES: A COMBINED MRI, NISSL AND ANTI-TYROSINE HYDROXYLASE (TH) IMMUNOFLUORESCENCE STUDY. Sinakevitch I, McDermott K, Khattab SO, Gray DT, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

Background: The Locus Coeruleus (LC) is a brainstem nucleus with the largest group of noradrenaline producing neurons. Dysregulation of LC systems contributes to cognitive dysfunctions in both healthy aged brains and brains that succumb to Alzheimer's disease. Notably, the LC is heterogeneous along the rostral-caudal and dorsal-ventral axes with respect to neuron morphology, projection targets, and vulnerability to the impact of normative brain aging and neurodegenerative disease. In previous studies in our laboratory, we identified three distinct subnuclei in the macaque LC: a medial nucleus that was confined to the central gray area, a lateral nucleus that lies outside of the gray area laterally and blends within the mesencephalic tract (me5), and a compact area within the medial nucleus.

Methods: In this study, we describe in detail the 3D anatomy of the LC nucleus using the Nissl, Tyrosine hydroxylase (TH)-immunoreactivity, and MRI data of one macaque. Next, we describe the neuroarchitecture of the long-range processes of TH-positive LC neurons in the midbrain. Finally, we establish a protocol using AMIRA software for counting cells along the rostral-caudal axis and within the described compartments of LC. AMIRA software was employed to reconstruct the LC from the TH-immunofluorescence and Nissl sections that were aligned with previously collected in vivo structural MRI data. The macaque LC proper nucleus extends approximately 2.4mm along the rostro-caudal axis with an overall volume up to 3mm³. We also found that the extranuclear LC processes extend laterally to an adjacent area in the midbrain and surrounds the lateral and dorsal superior cerebellar peduncle. AMIRA software was also used to analyze the cell counts in each compartment.

Results: To accomplish this, LC TH-positive cells were first segmented manually to determine the range of possible cell dimensions to use for later segmentation. Next, all TH-positive neurons and processes were segmented using automatic AMIRA procedures, and the previously established cell dimensions were used to select putative cells within LC compartments. These automatic cell counts were compared with manual cell counts from within the LC nucleus to verify their accuracy.

Conclusions: In conclusion, this analysis pipeline will allow us to standardize our data on adult and aged macaques to find out the specific sites of vulnerability along the rostral-caudal axis of the LC compartments. Further neuronal analyses will be aimed at understanding the mechanisms responsible for LC vulnerability and its impacts on cognition in normative aging and disease.

ABERRANT FATTY ACID DEGRADATION BY ASTROCYTIC MITOCHONDRIA AS A MECHANISM OF BRAIN LIPID DROPLET ACCUMULATION AND LIPID DYSHOMEOSTASIS.

Qi G, Mi Y, Jin Y, Gu H, Yin F. University of Arizona; Florida International University; Arizona Alzheimer's Consortium.

Background: Abundant clinical evidence has demonstrated disrupted lipid homeostasis—including the accumulation of lipid droplets (LDs)—in early stages of Alzheimer's disease (AD), and a variety of lipid metabolism genes have been identified as top risk factors of the disease. Nevertheless, how lipid dyshomeostasis and LD accumulation emerge in the degenerating brain remain elusive. Fatty acids (FAs) are the essential building blocks for nearly all lipid classes. We reported previously that APOE- ϵ 4 (ApoE4), the greatest genetic AD risk factor, induces a metabolic shift in astrocytes towards diminished FA degradation and elevated LD accumulation. Further, FA degradation enzymes are highly enriched in astrocytic mitochondria relative to neuronal mitochondria, indicating a role of astrocytic mitochondria in brain lipid metabolism.

Methods: Here, by using a mouse model of astrocyte specific suppression of oxidative phosphorylation (OxPhos), we show that while mitochondrial OxPhos is dispensable for the astrocytic bioenergetics and survival, it is indispensable for the degradation of FA and protects the brain from lipotoxicity. Lipid droplet (LD) formation, lipid metabolism, fatty acid (FA) metabolism, and mitochondrial function were determined in mouse brain and astrocytes isolated from mice with astrocytic deletion of transcription factor A mitochondrial (TfamAKO).

Results: TfamAKO induced accumulations of free FAs and neutral lipids including triacylglycerol and cholesteryl esters, which were paralleled with abundant astrocyte-located LDs in the hippocampus, and to a lesser extent, the cortex. Astrocytic mitochondrion-initiated perturbation to brain lipid homeostasis was further characterized by a targeted lipidomic panel, with 101 of the 153 detected lipid species differentially expressed in TfamAKO brains relative to wildtype controls, including increased levels of ceramide species and decreased levels of phosphatidylserine and phosphatidylinositol species. Our findings suggest that although astrocytic mitochondria are functionally less active (lower OxPhos activity) and bioenergetically less significant (less ATP production) than their neuronal counterparts, a modest level of OxPhos activity is required for the degradation of FA and hence the homeostasis of all lipid classes in the brain.

Conclusions: These data provide new insights into the unique role of astrocytes in maintaining brain lipid homeostasis, and potentially, in protecting the brain from lipid-involving neurodegenerative disorders.

This work has been supported by the National Institute on Aging (NIA) grants RF1AG068175 to FY, P01AG026572 (Project 1 and Analytic Core to FY), and Arizona Alzheimer's Consortium Pilot Project grants to FY.

ACCELERATED MIDLIFE AGING IN hAPOE ϵ 4/4 FEMALES. Wang T, Mao Z, Delatorre N, Wiegand JP, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.

Background: Age, female sex and APOE ϵ 4 genotype are the greatest Alzheimer's (AD) risk factors, with a stronger APOE ϵ 4 link to AD in women. The APOE-sex interaction is also evident in hAPOE mouse models where APOE ϵ 4 induces more severe neurodegeneration and cognitive deficits in female mice. However, the mechanisms by which these two risk factors converge to disrupt brain function remain elusive.

Methods: To investigate effect of APOE genotype on midlife endocrine aging, 6-, 9- and 15-month hAPOE ϵ 3/3 and hAPOE ϵ 4/4 female mice were stratified into 3 different endocrine aging groups based on vaginal cytology profiles: regular cyclers (consistent 4–5 day cycles), irregular cyclers (of 6–9 day cycles), and acyclic (no cycling >9 days). Plasma levels of metabolomic makers were measured. Brain mitochondrial function was quantified.

Results: hAPOE ϵ 4/4 females exhibited accelerated endocrine aging evidenced by increased magnitude of brain metabolic defect coupled with inability to mount an adaptive bioenergetic response. Systems biology of endocrine aging initially identified in perimenopausal rat model were replicated in the hAPOE ϵ 3/3 mouse model. In contrast, hAPOE ϵ 4/4 females exhibited accumulation of adipose tissue with high plasma triglyceride and accelerated ketone body dysregulation during perimenopausal transition, indicating deficits in adaptive metabolic response required for sustaining brain metabolic demand during aging. Further, hAPOE ϵ 4/4 females exhibited greater perimenopause- and menopause-induced brain mitochondrial dysfunction.

Conclusions: Outcomes of these analyses provide a plausible mechanistic pathway underlying the greater risk of AD in APOE ϵ 4 females. Further, these data indicate that the bioenergetic crisis underlying metabolic reprogramming in brain are greater in the APOE ϵ 4 female brain while compensatory adaptive responses are compromised. These findings provide a rational mechanistic precision medicine approach to intervene during midlife to prevent or delay the onset of the prodromal / preclinical stage of AD.

AGE- AND AGING-WITH-INJURY-RELATED TEMPORAL MICROGLIAL MORPHOLOGICAL PROFILES INDICATE UNIQUE PATHOLOGICAL PROCESSES IN BEHAVIORALLY RELEVANT CIRCUIT RELAYS. Krishna G, Sanghadia C, Sabetta Z, Rajaboina B, Adelson PD, Thomas TC. University of Arizona College of Medicine-Phoenix; Barrow Neurological Institute at Phoenix Children's Hospital; Phoenix VA Healthcare System; University of Arizona; Arizona State University; Arizona Alzheimer's Consortium.

Background: Traumatic brain injury (TBI)-induced chronic neuroinflammation is implicated in the development of persisting neurological morbidities and age-related neurodegenerative diseases. A chronic time course of neuroinflammation in a behaviorally relevant circuit in both sexes is needed to accurately and comprehensively assess the benefits and consequences of neuroinflammation. We used a temporal profile for structural, molecular, and functional mechanisms contributing to late-onset persisting sensory hypersensitivity in the rat whisker-barrel circuit (WBC) relays to assess neuroinflammation.

Methods: Age-matched male and female Sprague-Dawley rats underwent midline fluid percussion injury (FPI) or sham surgery (n = 5-6/group; total = 64). At 7-, 56-, and 168-days post-injury (DPI), Iba-1 stained morphologies and morphological characteristics were quantified in cortical and thalamic WBC relays followed by three-way ANOVAs (FPI, DPI, Sex).

Results: In the cortex and thalamus, microglia had shorter branches and fewer endpoints, indicative of microglial activation, as a function of FPI ($p < 0.05$), DPI ($p < 0.05$), and FPI \times DPI ($p < 0.05$), where FPI-induced activation decreased and age-related activation (shams) increased over time. By 168DPI, sham and FPI morphological characteristics were similar; However, hyper-ramified microglia increased in sham versus FPI ($p < 0.05$). Cortical rod microglia were highest at 7DPI ($p < 0.05$) and present through 168DPI (FPI \times DPI interaction; $p < 0.05$). FPI \times DPI \times Sex interaction for thalamic cell counts ($p < 0.05$) indicated a greater FPI response in 7DPI males versus females ($p < 0.05$).

Conclusions: Chronic TBI-induced neuroinflammation has a distinct regional and sex dependent temporal profile compared to age-related neuroinflammation, providing a template for more comprehensive interpretation of the impact of intervention on specific pathological processes associated with aging- and aging-with-injury-related morbidities.

AGE-RELATED CHANGES IN PERFORMANCE ON THE FRONTAL CORTEX-DEPENDENT TEMPORAL ORDER MEMORY TASK. Guswiler O, Khattab S, Bohne K, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

Background: It is known that cognitive performance declines with normative aging in several domains, but few studies have attempted to tease apart the specific regions that may be more susceptible to or robust against age-related changes over time. The temporal order memory (TOR) task is a simple and efficient test used to assess recognition memory, specifically the ability to recall when an object or event was committed to memory. In aging humans, prefrontal cortex-dependent memory exhibits some of the most dramatic and early changes relative to other brain functions (Park et al., *Psychology and Aging*, 2002, 17:299). Previous work has shown that lesions to the medial prefrontal cortex (mPFC) significantly disrupt performance on this task in young rats (Barker et al. *J. Neurosci*, 2007, 27:2948). Although the TOR task has been utilized in many studies, there has been little to no research on the effect of age on performance.

Methods: We therefore investigated the sensitivity of the TOR task to detect age differences in a rodent model of normative aging. We tested male Fischer 344 (F344) rats of two separate ages, young (9mo) and old (23-27mo). Animals were exposed to the test box for 10 minutes for two consecutive days. On days 3 and 4, they were exposed first to two identical objects (i.e., A and A) for 4 minutes. One hour after this, the rats were exposed to two different identical objects (i.e., B, B) for 4 minutes. Two hours following the second sample phase, the test phase began during which the rat was presented with one copy of both objects (i.e., A and B). In adult rats, the object from the first sample phase (A) is explored more, indicating that the rat recognizes that this object was explored during a temporal window that was more remote than the second object explored.

Results: Our results indicate a trend for the aged rats to be impaired compared to the younger animals in their ability to recognize which object was most recently experienced.

Conclusions: This simple temporal order memory task will be extremely useful for further exploration of the differences between young and aged individuals, particularly in combination with high-density cell recordings in the mPFC and related structures.

APOE AND CLU COOPERATIVELY PROMOTE AMYLOID FORMATION. Ding Z, Haug KA, Fryer JD. Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Apolipoprotein E (APOE) and clusterin (CLU) are critical in the pathogenesis of Alzheimer's disease (AD). Common coding variants in APOE (e.g., APOE4) impart at least 3-fold higher risk of developing AD, while common noncoding variants in CLU impart smaller but still highly significant risk for AD. Using genetically engineered mouse models lacking either APOE or CLU, previous studies from our lab and others have shown that both are critical in the formation of amyloid. However, only a single published study has examined the combined effects of APOE and CLU in a mouse model of amyloidosis.

Methods: We generated mice that lacked both murine APOE and CLU (double knockout mice) on the APP/PS1 background of AD amyloidosis. We assessed these mice using histological analysis as well as single-cell RNAseq profiling from brain tissue.

Results: Compared to APP/PS1 controls, we found that double knockout mice for both APOE and CLU had a striking reduction in the amount of amyloid plaques in the cortex. Moreover, we found that these double-knockout mice were completely void of amyloid plaques in the hippocampus. Single-cell RNAseq experiments revealed a strong reduction in the amount of activated microglia in these double knockout mice.

Conclusions: Contrary to a previous study that reported increased amyloid load in APOE^{-/-};CLU^{-/-} double knockout mice, we found a dramatic reduction in amyloid plaques and a concomitant loss of activated microglia when using genetically inbred (C57BL/6J) mouse lines. Further studies are needed to determine whether these effects are cell-type specific (e.g. astrocyte-derived APOE and CLU conditional knockouts) or whether these lipoproteins have synergistic roles in tau pathology.

ASSESSMENT OF FINGER TAPPING ABNORMALITIES IN OLDER ADULTS WITH MEMORY COMPLAINTS. McElvogue MM, Steffes L, Burke A, Stokes A, Prigatano GP. Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Subjective complaints of impaired memory and cognitive decline are common concerns in aging populations, though scores on psychometric tests of memory and cognitive function can vary greatly. Patients who complain of memory impairment but demonstrate normal performance on memory tests may be classified as having subjective memory complaints (SMC), while patients who exhibit an objective decline in memory can be classified as having mild cognitive impairment (MCI). Recent studies have shown that Alzheimer's disease (AD) may present with subset disorders of motor functioning, including finger tapping abnormalities. Measures such as speed of tapping, inter-tap intervals, and individual variability of finger tapping scores were shown to separate healthy older individuals from those with AD and MCI. Such findings suggest that finger tapping measures may have diagnostic value for separating patients with SMC from AD and MCI and may be useful in identifying which patients may progress to AD.

Methods: This study included 4 groups of participants, comprised of 8 healthy controls (HC 3 males; 73 +/- 7 years), 12 SMC (3 males; 69 +/- 5 years), 12 MCI (7 males; 76 +/- 5 years), and 7 early AD (5 males; 75 +/- 6 years). A standard clinical neuropsychological examination was conducted for all patients to confirm their cognitive status. All participants underwent the BNI Screen for Higher Cerebral Functions (BNIS) and the modified version of the Halstead Finger Tapping Test (HFTT). Metrics obtained from the HFTT include mean and range of tapping scores, number of invalid taps, and number of inhibition failures across 7 trials in each hand. ANOVA was performed for the BNIS score and HFTT metrics with the main effect of group. Tukey HSD tests were used for post hoc comparisons between groups.

Results: There was no significant difference across groups for age or education level, except for a significant difference in age between SMC and MCI cohorts ($p = 0.02$). There was a significant effect of group on BNIS score, with significantly lower BNIS scores in AD ($p < 0.001$ for all) than in SMC and HC, as well as in MCI than in SMC and HC, which is consistent with expected psychometric test results for each group. HFTT tapping scores were not significantly different across groups in the right hand ($p = 0.32$) or the left hand ($p = 0.199$). The number of invalid taps was significantly different across groups for both hands, where post hoc comparisons indicated that the number of invalid taps in the right hand was significantly higher in AD than SMC ($p = 0.002$) and HC ($p = 0.014$) cohorts. The number of invalid taps in the left hand was significantly higher in AD and MCI than SMC ($p = 0.015$ and $p = 0.010$, respectively), with no significant differences found between HC and all other groups. No significant difference was found for HFTT range of tapping scores in the right hand, though the range was significantly increased for the left hand in AD compared to SMC ($p = 0.002$) and HC ($p = 0.004$) cohorts.

Conclusions: Preliminary analysis demonstrates the potential of the modified HFTT task in assessing neuropsychological impairment in aging populations. Data collection is ongoing in each cohort, and further analysis will establish the relationship between these metrics and cognitive status. Abnormal finger movements, especially invalid tapping movements in the left hand, may distinguish patients with MCI and AD from patients with SMC. As motor scores are relatively understudied in cognitively impaired populations, these novel assessments may lend unique insight into the role of AD pathology on fine motor control and coordination, executive functional control, and visuospatial processing.

ASSOCIATION OF APOE E4 WITH DECREASED EMOTIONAL PRECISION OF WORD USE IN NON-DEMENTED OLDER ADULTS. Stoica T, Grilli MD, Andrews-Hanna J. University of Arizona; Arizona Alzheimer's Consortium.

Background: The present study examines whether the well-known “positivity effect” exhibited by older adults includes emotional precision of word use (affective lexical granularity) during naturalistic verbalization (resting state cognition). Despite the prevalence and potential importance of resting state cognition on daily functioning and psychological wellbeing, no study has yet probed whether older age is associated with an increase in granularity during such mental states. Moreover, it is unknown whether APOE ε4 carrier status influences emotional precision of word use.

Methods: Across three separate studies, we asked a total of 77 young adults and 141 cognitively normal older adults to speak their thoughts freely out loud (Think-Aloud Paradigm) and assessed whether any age differences existed in affective lexical granularity. Additionally, we investigated whether APOE ε4 carrier status had any effect on this novel quantification of emotional thought.

Results: Age difference analyses showed that older adults exhibit higher negative and positive lexical granularity compared to younger adults. Within older adults only, we show that APOE ε4 carriers exhibit less negative granularity than noncarriers.

Conclusions: These novel results firstly suggest that normal cognitive aging is associated with an increase in the use of unique positive words during natural periods of restful thought, and therefore reveal a novel contributor to the “positivity effect” witnessed in this population. Secondly, these findings indicate that older adults that are APOE ε4 carriers exhibit less negative granularity, which could be tied to a decrease in psychological wellbeing. Together, these data may have implications for clinical populations whose natural thought content may differ.

ASTROCYTIC MITOCHONDRIAL DYSFUNCTION INDUCES NEURODEGENERATION THAT RESEMBLES ALZHEIMER'S DISEASE. Mi Y, Qi G, Vitali F, Shang Y, Raikes AC, Wang T, Brinton RD, Yin F. University of Arizona; Arizona Alzheimer's Consortium.

Background: Mitochondria are the major cellular sources of ATP via oxidative catabolism of glucose or alternative fuels. A bioenergetic deficit, encompassing a decline in mitochondrial bioenergetic function and glucose hypometabolism, is associated with brain aging and emerges in early stages of neurodegenerative diseases including Alzheimer's disease (AD). However, the metabolic profile of brain cells is highly diverse with different cell types manifesting differential fuel preference and susceptibility to mitochondrial phenotypic changes. Across cell types, mitochondrial dysfunction in neurodegeneration has been best documented in neuron, and more recently in microglia, yet the pathological role of mitochondria in astrocyte, the most abundant cell type in the brain, remains to be defined.

Methods: To determine whether astrocytic mitochondrial dysfunction can induce neurodegeneration, we crossed mice with loxP-flanked Tfam (Tfam^{lox/lox}) with the GFAP-Cre 77.6 mice to generate the GFAP-Cre:Tfam^{lox/lox} mice, in which transcription factor A mitochondrial (Tfam) is deleted selectively in astrocytes (TfamAKO). Behavioral, electrophysiological, immunostaining, and magnetic resonance imaging analyses were employed to characterize cognitive function and other AD-related phenotypes of these mice.

Results: Astrocytic mitochondrial dysfunction triggered by TfamAKO is sufficient to induce neurodegeneration resembling AD. In the TfamAKO mice at 6-month-of-age, deficits in recognition memory and exploratory behavior were accompanied by a decline in hippocampal long-term potentiation and reduced synaptic density and dendrite complexity. These mice were also characterized by strong reactive astrogliosis, microglial activation, and elevated levels of pro-inflammatory cytokines in the hippocampus and cortex. Moreover, TfamAKO mice exhibited significantly decreased indices of white matter microstructure and myelin integrity, including lower fractional anisotropy and lower diffusivities.

Conclusions: Our data show that astrocytes with dysfunctional mitochondria induce neurodegeneration that recapitulates critical features of AD and thus suggest astrocytic mitochondria as a previously underappreciated contributor to the metabolic and functional changes implicated in neurodegenerative diseases.

This work has been supported by the National Institute on Aging (NIA) grants RF1AG068175 to FY, P01AG026572 (Project 1 and Analytic Core to FY), Arizona Alzheimer's Consortium Pilot Project grants to FY, and the Packer-Wenz research endowment to FY.

BLOOD-BASED PROTEIN VARIANT BIOMARKER PANEL FOR EARLY DIAGNOSIS OF ALZHEIMER'S DISEASE. Schulz P, Cho HJ, Venkataraman L, Sierks MR. Arizona State University; Arizona Alzheimer's Consortium.

Background: Biomarkers that can facilitate pre-symptomatic diagnosis of Alzheimer's disease (AD) and distinguish it from other dementias would be extremely valuable clinical tools. Therapeutic intervention for patients with Alzheimer's disease (AD) should be most effective if begun early before significant neurological damage has taken place. The two most promising fluid biomarkers for AD to date are variants of A β and tau, in particular the 42 amino acid variant of A β (A β 42) and the phosphorylated variants of tau, however these protein variants are also present in cognitively normal individuals and are not the relevant toxic protein species responsible for neurodegeneration. Small soluble oligomeric forms of A β , tau and TDP-43 are widely considered to be the relevant toxic protein variants and represent promising early stage biomarkers for AD. We generated a novel panel of 9 antibody fragments (scFvs) that selectively recognize different A β , tau and TDP-43 variants that are uniquely present in human AD brain tissue and blood samples. We utilized this scFv panel to characterize the protein variant profiles of longitudinal human plasma cases from 50 patients where 25 converted to AD during the study. One inherent problem in identifying early biomarkers for AD is that 20 to 40% of the elderly control cases are expected to be presymptomatic for AD and related dementias (ADRD). Here we show that a panel on reagents binding AD specific protein variants can very effectively diagnose early stage presymptomatic AD cases from control cases and also identify the control cases that are likely at high risk of getting AD.

Methods: We utilized a sensitive sandwich ELISA developed in our lab to detect biomarker variants from blood plasma. The nine different scFvs were used as capture antibodies and a phage display version of a pan specific anti-A β , tau or TDP-43 scFv was used as a detection antibody. Bound detection phage were identified using avidin-HRP and measured by ECL. One-tailed bivariate correlations at $p < 0.05$ were completed using SPSS and statistical significance based on independent samples t-tests at $p < 0.05$. Receiver operational characteristics (ROC) curves were also generated using SPSS.

Results: Seven of the nine scFvs utilized showed significant differences in target protein variant levels between the plasma samples from the AD cases compared to cognitively normal cases including two A β variants (C6T and E1), four tau variants (D11C, ADTau2, ADTau4 and ADTau6) and the TDP-43 variant (AD-TDP3) with a sensitivity of 92% and a specificity of 76%. To identify early stage AD biomarkers, we divided the plasma samples collected from patients that converted to AD into three groups: 1) samples collected prior to clinical diagnosis of MCI (pre-MCI). 2) samples collected after diagnosis of MCI but before AD, and 3) samples collected after diagnosis of AD. We analyzed results obtained comparing only the preMCI plasma samples from the AD cases to the control cases and six of the nine scFvs still showed statistically significant differences (C6T, D11C, ADTau2, ADTau4 and ADTau6, ADTDP3). Using the ROC analysis and Youden's index to calculate an optimal threshold cutoff for our antibody panel, we identified 5 out of 25 control cases that had protein variant profiles similar to the preMCI profiles of the AD cases and likely represent presymptomatic ADRD cases. Removing these 5 flagged control cases from the control pool, the scFv panel had a sensitivity of 84% and specificity of 100% when comparing plasma samples from the AD and control cases when all of the cases were still presymptomatic.

Conclusions: A simple blood based assay using a panel of reagents targeting protein variants selectively present in human AD samples, can diagnose early presymptomatic AD cases with high sensitivity and specificity.

CAREPLACE: AN INNOVATIVE COMMUNITY BASED CARE COORDINATION PROGRAM TO ADDRESS UNMET CAREGIVER NEEDS, A PILOT STUDY. Buchanan BL, Reynolds L, Bordenave E. AT Still University.

Background: Nearly 42 million family caregivers in the United States are providing unpaid care to individuals ages 50 and older with dementia or other chronic health conditions. Only 30% of caregivers report receiving the support they need from the healthcare system. Caregivers do not feel they have the education and training to effectively complete their role and are unsure of services that could benefit them. Traditional practice and reimbursement restricts addressing caregiver needs to those directly associated with the patient and leaves the caregiver's needs not fully addressed. The CarePLaCe program was designed to support caregivers in their role caring for an adult over 60, living with dementia and/or another chronic health condition. The program includes an initial evaluation, a home safety assessment, and the development and delivery of an individualized Care Plan which includes educational/skills training modules for the caregiver. CarePLaCe caregiving dyads have access to clinical CarePLaCe personnel throughout and after the program components are completed for ongoing support and revisions to the Care Plan.

Methods: A pilot study was done using quantitative data from the Adult Carers Quality of Life Questionnaire (AC-QoL), and qualitative data from individual interviews. Eight participants, 18 years of age and older, living with and caring for someone ≥ 60 years of age with a chronic condition completed the CarePLaCe program. Individual interviews were conducted after program participation consisting of structured questions to assess effectiveness of program elements in meeting caregiver needs. This study of CarePLaCe sought to: 1) Evaluate pre and post changes in caregiver quality of life using the AC-QoL, 2) Assess effectiveness of recruitment strategies to inform number of participants needed for larger study, 3) Assess caregiver perceptions of effectiveness of program elements, and, 4) Use data to inform effect size and complete power analysis for optimal sample size for larger study.

Results: When evaluating changes in caregiver quality of life before and after the program, six of the eight AC-QoL subscales showed improvements in quality of life, and two showed decreases. Qualitative analysis of caregiver perceptions of the effectiveness of the CarePLaCe program indicated most participants had positive perceptions. Thematic analysis of the interviews found five themes: benefit of an outside perspective, needed information and resources provided, having a support system, reduced stress, and improved self-efficacy.

Conclusions: The overall purpose of assessing the feasibility of conducting an intervention study of CarePLaCe was met. Results of the current pilot study seemed to meet 3 of the 4 original aims, which were intended to inform a larger intervention study. Changes in AC-QoL scores from preprogram to post-program participation showed improvement in 6 of 8 quality of life areas. Caregiver perceptions of program effectiveness, as well as additional elements to include in the program, were reported in individual interviews. Effect sizes and a power analysis were completed to determine an optimal sample size in a larger study.

CAREPRO SPANISH: A VIRTUAL INTERVENTION FOR THE LATINO COMMUNITY.
Gonzalez-Pyles S, Covarrubias A, Carbajal B, Carbajal L, Córdova L, Pérez S, Manzo A, Coon DW. Arizona State University; Arizona Alzheimer’s Consortium.

Background: Between now and 2025, Arizona is projected to have the greatest increase in its proportion of both people living with ADRD (33.3%) and their family caregivers (Alzheimer Association, 2021). Family caregiving for people with dementia leads to a host of negative outcomes including poorer emotional well-being and physical health outcomes as well as lowered income and financial health (see Alzheimer’s Association 2020 for a review). These negative outcomes increase caregiver need for and use of health and social services (Kasper et al., 2015; Stall et al., 2019). During unusual circumstances—such as pandemics or other situations that limit care recipient normal daily routines—caregiver outcomes are likely to be impacted further and new, innovative models of intervention are needed. The COVID pandemic provided a unique opportunity to adapt existing evidence-based family caregiver intervention programs (e.g., CarePRO; Coon et al., 2012) for video-conferencing platforms such as Zoom.

Methods: CarePRO Virtual Spanish (CarePRO-V SPA) is a virtual adaptation of the recognized evidence-based caregiver intervention CarePRO (Care Partners Reaching Out). CarePRO-Virtual Spanish 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 to overcome daily stressors resulting from their caregiving. Between sessions, a designated coach meets with each participant, individually, for skill-reinforcement and feedback. Pre/post outcomes were derived through individual telephone assessments lasting about 60 minutes pre- and post- intervention.

Results: Twenty-five self-identified Latinas participated in the CarePRO-V SPA intervention and twenty completed all group sessions and telephone coach calls suggesting reasonable acceptability and feasibility. Delivery was successful within Arizona and outside the state including one participant outside the continental US. Caregivers reported strong overall benefit from the workshop (94.7%). In addition, they stated the workshop helped: enhance their ability to care for their loved one (100%); increase their understanding of memory loss (89.4%); kept their loved one living at home (89.4%); and, made their lives easier (84.2%). The majority of participants also reported improvements in: their own overall confidence in care provision (89.4%); their level of preparation to provide care in the future (89.4 %); their own mood or emotional well-being (84.2%); and bother associated with their loved one’s behavioral changes (78.9%). Based on feedback, participants expressed interest in joining similar projects offered by our team in the future. Challenges with technology did occur but these challenges were isolated to caregivers with limited experience with technology.

Conclusions: Data collected from the Zoom-based delivery of the evidence-based intervention CarePRO in Spanish suggests both feasibility and acceptability. Caregivers reported high levels of perceived benefit from the intervention. Next steps include analysis of pre/post intervention survey data designed to assess changes in mood, coping, social support, and other quality of life outcomes. These results will help shape applications for future intervention research with this population.

CASE REPORT: A SEVERE REACTION TO MRNA SARS-COV-2 VACCINE BOOSTER IN AN APOE-EPSILON 4 CARRIER WITH MILD ALZHEIMER'S DISEASE RECEIVING ADUCANUMAB IN A CLINICAL TRIAL. Restifo LL, Erickson RP. University of Arizona College of Medicine-Tucson; University of Arizona; Arizona Alzheimer's Consortium.

Background: This case represents the convergence of two timely elements. It is important to document adverse events associated with the new COVID-19 vaccines, especially when they impact activities of daily living and the patient has an unusual medical history. While ARIA-E (amyloid-related imaging abnormalities – edema) is a common occurrence in trial participants administered aducanumab, especially in those who carry APOE- ϵ 4, much remains to be learned about its etiology and risk factors.

Methods: A woman in her seventies had two weeks of fever and flu-like symptoms starting abruptly several hours after the simultaneous administration of a Pfizer BioNTech BNT162b2 booster for Sars-CoV-2 and the influenza vaccine. Laboratory tests showed markedly elevated alkaline phosphatase and glutathione transferase, consistent with cholangitis, while other chemistries and blood counts were within normal range. Past medical history included APOE- ϵ 4 carrier genotype, mild Alzheimer's disease, for which she was receiving monthly aducanumab infusions in a clinical trial (NCT04241068), and resolving polymyalgia rheumatica (PMR).

Results: Over a two-week period, the patient gradually recovered with at-home supportive care, completing a one-year tapering course of prednisone. The patient reports, "I lost two weeks of my life." She had a brief recurrence of PMR about two months after the vaccinations. It is also noteworthy that she had two bouts of aducanumab-associated ARIA-E, before and following the infusion immediately after the acute episode, the latter lasting two months. Both were asymptomatic, without microhemorrhages, seizures, or changes in neurological exam. Once the second bout of ARIA-E resolved, she resumed monthly aducanumab infusions, as per the clinical trial protocol.

Conclusions: This case raises many questions. Research is needed to explore the interactions among autoimmune disease, exposure to anti-amyloid monoclonal antibodies, and inflammatory adverse events following Sars-CoV-2 mRNA vaccination.

CEREBRAL MICROVASCULAR DYSFUNCTION IN 5X-FAD MICE: ROLE OF BIOLOGICAL SEX, BK CHANNEL ACTIVITY AND OXIDATIVE STRESS. Silva JF, Savu A, Polk FD, Kath AM, Pires PW. University of Arizona College of Medicine, Tucson; Arizona Alzheimer's Consortium.

Background: Vasculopathy is present in patients with Alzheimer's disease (AD) and it may contribute to disease progression and severity, via poorly understood mechanisms. Markers of oxidative stress are present in the brain of AD patients, as well as in transgenic mouse models. This increase in reactive oxygen species can lead to oxidative damage in macromolecules, including proteins, which can alter their function. Large conductance calcium activated K⁺ channels (BKCa) are one of such targets in vascular smooth muscle cells; these channels play an important role in vasodilatory responses and maintenance of myogenic tone in resistance arteries. Opening of BKCa channels occurs upstream from localized intracellular Ca²⁺ release events (Ca²⁺ sparks), and results in K⁺ efflux, vascular smooth muscle cell hyperpolarization and vasorelaxation. In a pro-oxidative scenario, BKCa can be oxidized, resulting in decrease activity and exacerbation of contractile responses, which can compromise cerebral blood flow regulation, generating an environment that may accelerate neurodegeneration. We hypothesized that reduction in BKCa-dependent vasodilation in cerebral arteries, as consequence of oxidative stress, results in neurovascular dysfunction in the 5x-FAD model of AD.

Methods: Posterior communicating arteries (PComA) from 5 months-old male and female 5x-FAD and wild-type (WT) littermates were isolated and studied in ex vivo using pressure myography. Calcium (Ca²⁺) sparks in smooth muscle cells were evaluated by spinning-disk confocal microscopy. Oxidative stress levels were assessed by total and oxidized glutathione levels in the brain using a colorimetric enzymatic assay. Basal cortical perfusion and functional hyperemia were evaluated by laser speckle contrast imaging. Data are means ± SEM, analyzed by two-tailed Student's t-test.

Results: In females, PComA from 5x-FAD showed higher spontaneous myogenic tone than WT (Myogenic tone: 24.48 ± 3.20 vs 16.09 ± 0.93%, 5x-FAD vs WT, p < 0.05, N = 7). Constriction to iberiotoxin (30 nM, BKCa blocker) was smaller in 5x-FAD than WT, suggesting lower basal BKCa activity (Vasoconstriction: -4.252 ± 0.429 vs -9.220 ± 2.556%, 5x-FAD vs WT; p < 0.05; N=5), which was independent of alterations in intracellular Ca²⁺ sparks activity (Frequency: 0.51 ± 0.30 vs. 0.62 ± 0.33 Hz, 5x-FAD vs WT, p > 0.05, N=3-4). No differences in constriction induced by 60 mM KCl or endothelin-1 (30 nM) were observed in PComA from 5x-FAD when compared to WT. These vascular changes were associated to higher levels of oxidative stress in whole brain homogenates of 5x-FAD ([oxidized glutathione]: 7.83 ± 0.62 vs 5.27 ± 0.74 μM, 5x-FAD vs WT, p < 0.05, N=8), lower resting cortical perfusion atop the frontal cortex (Perfusion: 345.9 ± 16.43 vs. 415.5 ± 23.15 PU, 5x-FAD vs WT, p < 0.05, N = 6), and impaired functional hyperemia responses after whisker stimulation (increase from baseline: 3.82 ± 0.64 vs. 9.91 ± 1.41%, 5x-FAD vs WT, p < 0.05, N = 6). No significant differences were observed between male 5x-FAD and WT for all parameters studied.

Conclusions: Cerebrovascular impairments were more pronounced in female 5x-FAD mice, observed as an increase in spontaneous myogenic tone, likely due to reduction in smooth muscle cell BKCa activity associated to an increase in brain oxidative stress. These alterations were linked to reduced basal cortical perfusion and blunted neurovascular coupling responses.

CHARACTERIZATION OF BACTERIAL 16S RRNA GENE SEQUENCES EXTRACTED FROM POST-MORTEM BRAIN TISSUE OF AD PATIENTS AND CONTROLS. Jentarra G, Wilkey B, Chu P, Gonzalez F, Rogers A, Vallejo J, Jones D, Lynch L, Jones TB. Midwestern University; Arizona Alzheimer's Consortium.

Background: Published reports indicate that amyloid beta has strong activity as an antimicrobial peptide, leading to speculation that microbes may somehow be involved in the development of Alzheimer's disease (AD) pathology. We have previously found evidence of low levels of bacterial DNA in the brain tissue of AD patients and controls. In the current experiments, we sought to determine what the predominant taxa are in brain tissue and evaluate whether there were significant differences in those taxa between brain regions and between AD and mild cognitive (MCI) patients and two groups of non-demented control individuals. 16S rRNA gene sequencing analysis was used on post-mortem brain tissue samples from Alzheimer's disease (AD) patients and a variety of control individuals with varying pathology and cognitive symptoms.

Methods: DNA was extracted from the post-mortem brain tissue of 48 subjects, including 12 AD patients, 12 patients with mild cognitive impairment (MCI), 12 individuals with significant AD-associated pathology but no cognitive deficits (high pathology controls), and 12 non-demented normal control individuals. Two brain regions from each subject were analyzed, the superior frontal gyrus (SFG) and the inferior temporal gyrus (ITG). 16S rRNA gene sequencing and basic bioinformatic analyses were performed by TGen in Flagstaff, AZ. Explicit 16S rRNA analysis software was used for general comparisons between brain regions and subject groups. For statistical analysis, commonly used microbiome methods were compared to a more recently published method, which was proposed to be more robust to low microbial biomass tissues.

Results: Post-mortem brain tissue samples from both the SFG and ITG are dominated by the presence of 5 phyla: Actinobacteria, Bacteroidetes, Cyanobacteria, Firmicutes, and Proteobacteria. Proteobacteria is the predominant phyla in both regions, making up an average of 52% of bacterial sequences in the SFG and an average of 75% in the ITG. These averages were relatively consistent amongst all subject groups. In the SFG for all subject groups, 60-75% of sequences were from gram negative bacteria, while 80-90% of sequences in the ITG were from gram negative bacteria. The frequent appearance of Cyanobacteria DNA in brain tissues was somewhat unexpected. Overall, roughly 25% of subjects had significant amounts of DNA from Cyanobacteria, and the relative abundance in samples was found to be much higher in the ITG. Principal components analysis found that the Proteobacteria and Firmicutes most strongly distinguish ITG from SFG, and this was true regardless of whether data was considered as a whole or restricted to the 5 dominant phyla. The choice of statistical analysis method did not affect the overall findings.

Conclusions: Our finding of a predominance of Proteobacteria in brain tissue of AD patients and controls is consistent with the reports of other groups who have assessed the presence of bacterial DNA in brain tissue from AD patients, as well as reports from researchers who have studied the presence of bacterial gene sequences in brain tissue from patients with multiple sclerosis or schizophrenia. This would suggest that the presence of bacterial DNA in brain tissue is relatively normal, at least in aged individuals, and that certain phyla of bacteria are much more likely to be present in the brain. There were clear differences in the prominence of bacterial phyla found in the two brain regions, suggesting a variable which affects deposition. We also noted substantial inter-individual variability in each of our subject groups, which made it difficult to discern if there were differences in relative abundance of phyla between those groups. Larger sample numbers will be needed to make more accurate between-group comparisons.

CHRONIC COGNITIVE AND CEREBROVASCULAR FUNCTION FOLLOWING MILD TRAUMATIC BRAIN INJURY IN RATS. Griffiths DR, Law LM, Young C, Fuentes A, Truran S, Karamanova N, Bell LC, Turner G, Emerson H, Mastroeni D, Gonzales RJ, Reaven P, Quarles CC, Migrino RQ, Lifshitz J. Phoenix VA Health Care System; University of Arizona College of Medicine – Phoenix; Barrow Neurological Institute at Phoenix Children’s Hospital; Barrow Neurological Institute; Arizona State University; Arizona Alzheimer’s Consortium.

Background: Severe traumatic brain injury (TBI) results in cognitive dysfunction in part due to vascular perturbations. In contrast, the long-term vasculo-cognitive pathophysiology of mild TBI (mTBI) remains unknown. We evaluated mTBI effects on chronic cognitive and cerebrovascular function and assessed their interrelationships.

Methods: Sprague-Dawley rats received midline fluid percussion injury (N=20) or sham (N=21). Cognitive function was assessed (3- and 6-month novel object recognition (NOR), novel object location (NOL) and temporal order object recognition (TOR)). 6-month cerebral blood flow (CBF) and blood volume (CBV) using contrast MRI and ex vivo circle of Willis artery endothelial and smooth muscle-dependent function were measured.

Results: mTBI rats showed significantly impaired NOR, with similar trends (non-significant) in NOL/TOR. Regional CBF and CBV were similar in sham and mTBI. NOR correlated with CBF in lateral hippocampus, medial hippocampus and primary somatosensory barrel cortex while inversely correlating with arterial smooth muscle-dependent dilation. 6-month baseline endothelial and smooth muscle-dependent arterial function were similar among mTBI and sham, but post-angiotensin II stimulation, mTBI showed no change in smooth muscle-dependent dilation from baseline response, unlike the reduction in sham. mTBI led to chronic cognitive dysfunction and altered angiotensin II-stimulated smooth muscle-dependent vasoreactivity.

Conclusions: The findings of persistent pathophysiologic consequences of mTBI in this animal model add to the broader understanding of chronic pathophysiologic sequelae in human mild TBI.

CLINICAL PREDICTORS OF ALZHEIMER'S DISEASE DEVELOPMENT IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT USING SYNTHETIC DATA DERIVED FROM VETERANS AFFAIRS ELECTRONIC HEALTH RECORDS. Irwin CM, Tjandra D, Aggarwal V, Hu C, Giordani B, Wiens J, Migrino RQ. Phoenix VA Healthcare System; The University of Arizona College of Medicine – Phoenix; University of Michigan; MD Clone; Arizona Alzheimer's Consortium.

Background: Current methods of predictive modeling for Alzheimer's disease (AD) rely heavily on AD-specific biomarkers that are either difficult or costly to obtain. Use of electronic health record (EHR) data leverages extensive multidimensional data from routine care encounters that could be used to identify clinical conditions that predict AD conversion from mild cognitive impairment (MCI). Synthetic data derived from the original patient data very closely resemble the original data but are truly non-identifiable because individual data does not relate to any real individual. Our goal is to identify clinical predictors of MCI to AD conversion using synthetic data that closely resemble VA EHR data.

Methods: Synthetic data produced by MD Clone software derived from Veterans Affairs (VA) Corporate Data Warehouse (CDW) EHR data were used to construct our study's cohort. From a dataset of 1,998,650 unique patients, we included patients with an MCI diagnosis between the ages of 62 and 67 and at least 10 years of follow-up or conversion to AD within 10 years in our final cohort (N = 11,262). ICD-9/10 codes were used to categorize patient comorbidities either present or absent at time of MCI diagnosis. Demographics and commonly associated AD comorbid conditions for AD were used in the model. A multivariate Cox proportional hazard model with forward stepwise selection was used to develop a final model of independently predictive variables.

Results: In the 41,376 patients diagnosed with MCI the median age of MCI onset was 64.73 years (IQR: 63.04 – 66.68). Our final study cohort was predominantly white (77.1%) and male (97.0%). A total of 2,424 out of 11,262 (21.5%) patients converted from MCI to AD within 10 years. The median conversion time was 4.26 years (IQR: 2.03 – 6.55). Renal failure (HR: 1.83, 95% CI: 1.38 – 2.42), cerebral infarction (1.33, 1.17 – 1.52), liver disease (1.33, 1.16 – 1.52), sleep apnea (1.26, 1.15 – 1.38), type II diabetes (1.21, 1.11 – 1.32), depression (1.17, 1.07 – 1.27), hyperlipidemia (1.11, 1.01 – 1.23), age (1.26, 1.22 – 1.29), and BMI (0.95, 0.95 – 0.96) were independently predictive of AD conversion within 10 years. Heart failure, coronary heart disease, atrial fibrillation, atherosclerosis, myocardial infarction, hypertension, hypothyroidism, hyperthyroidism, osteoporosis, glaucoma, rheumatoid arthritis, history of smoking, and alcohol abuse were removed by forward stepwise selection from the final model.

Conclusions: Patient EHRs provide valuable information that can be leveraged to develop AD prediction models that may have clinical utility in identifying patients at high risk of AD. Use of synthetic data extend the ability to analyze non-identifiable data for model building but may encode incorrect assumptions. Our immediate next task is to validate the performance of the model using synthetic data with real patient data and to develop a predictive nomogram that can be used to estimate an individual patient's risk for AD conversion from MCI.

COGNITIVE HETEROGENEITY AND RISK OF PROGRESSION IN DATA-DRIVEN SUBTLE COGNITIVE DECLINE PHENOTYPES. Edmonds EC, Thomas KR, Bangen KJ, Weigand AJ, Ortiz G, Walker KS, Salmon DP, Bondi MW. Banner Alzheimer's Institute; University of Arizona; University of California, San Diego; VA San Diego Healthcare System; San Diego State University; Arizona Alzheimer's Consortium.

Background: There is increasing recognition of cognitive and pathological heterogeneity in early-stage Alzheimer's disease and other dementias. Data-driven approaches have demonstrated multiple cognitive phenotypes in those with mild cognitive impairment (MCI), but few studies have examined this heterogeneity and its association with progression to MCI/dementia in cognitively unimpaired (CU) older adults. We identified cluster-derived subgroups of CU participants based on comprehensive neuropsychological data, and compared baseline characteristics and rates of progression.

Methods: Hierarchical cluster analysis was conducted on baseline neuropsychological test scores from 365 CU participants (mean age=71.9 [SD=7.5] years; 55.9% female; 93.4% white; 15.6% Hispanic/Latinx) in the University of California San Diego (UCSD) Shiley-Marcos Alzheimer's Disease Research Center. Cox regression adjusting for age, education, sex, and ethnicity determined the risk of progression to (a) consensus diagnosis of MCI or dementia, or (b) a DRS score ≤ 129 , within an average of 6.25 years (range 1-20 years).

Results: Cluster analysis identified 5 groups: All-Average (n=139), Low-Visuospatial (n=46), Low-Executive (n=51), Low-Memory/Language (n=83), and Low-All Domains (n=46). Subgroups had unique demographic and clinical characteristics. Rates of progression to MCI/dementia were higher for the Low-Visuospatial (hazard ratio [HR] 2.39), Low-Memory/Language (HR 4.37), and Low-All Domains (HR 7.21) groups relative to the All-Average group. The Low-Executive group was also twice as likely (HR 2.03) to progress to MCI/dementia compared to the All-Average group, but did not statistically differ. The pattern of results was similar when a DRS ≤ 129 threshold was used to assess progression to cognitive impairment.

Conclusions: Differing rates of progression within CU subgroups suggest that there are multiple pathways and/or unique profiles of subtle cognitive decline that ultimately lead to a diagnosis of MCI/dementia. Use of comprehensive neuropsychological test batteries that assess several domains may be a key first step toward an individualized approach to early detection, with the goal of increasing opportunities for early intervention. Future studies will examine cognitive heterogeneity of CU participants within the Arizona Alzheimer's Consortium and associations with Alzheimer's disease biomarkers.

CRITICAL PATH FOR ALZHEIMER'S DISEASE (CPAD) CONSORTIUM: PRE-COMPETITIVE COLLABORATION TO ACCELERATE AND DE-RISK DRUG DEVELOPMENT IN ALZHEIMER'S DISEASE. Sivakumaran S, Cullen N, Priest E, Lau C, Karten Y. Critical Path Institute; Arizona Alzheimer's Consortium.

Background: The Critical Path for Alzheimer's Disease (CPAD) Consortium is a global, neutral convener, bringing together diverse stakeholders across industry, regulatory agencies, patient advocacy organizations and academia within a pre-competitive forum under a data-driven, regulatory framework to accelerate therapeutic innovation in Alzheimer's disease (AD). CPAD members, regulatory agencies (FDA, EMA), and CPAD's Quantitative Medicine Program collectively identify key questions and unmet needs in AD drug development. Using our core competencies in data management and standards, advanced quantitative analytics, biomarkers, clinical outcome assessment tools and regulatory science, we develop actionable solutions that help de-risk decision making in the AD drug development process.

Methods: Patient-level data and neuroimages are acquired from contemporary Phase II and Phase III AD clinical trials and observational studies, with emphasis on rich fluid and imaging biomarker information. After standardization, data are integrated into a database from which analysis-ready data subsets need to be generated, based on user-defined filters of baseline participant characteristics. We are developing a user friendly, web-based user interface called the "Actionable Data Model" (ADM) tool which will facilitate the generation of analysis-ready data subsets from the CPAD database, based on user-defined filters of baseline participant characteristics. The integrated data is used for development of a comprehensive set of disease progression models across the continuum of the disease. The models will serve as the basis for clinical trial simulation tools to facilitate informed decision making in the drug development process and optimize patient and endpoint selection and design of efficacy studies. To incorporate imaging biomarkers as key covariates in the disease progression modeling, we are developing post-acquisition data 'harmonization' tools and analysis methods that reduce variance across studies, sites, and scanners, while retaining the power to study complex disease related effects.

Results: As of May 2022, CPAD's clinical trial repository contains 61 studies with 42,043 individual anonymized patient records. A prototype ADM tool was built using Shiny Software from R Studio, allowing for initial data exploration and analysis subset creation. Analysis subsets were used to develop a preliminary set of disease progression models that characterize the time course of clinically relevant measures (clinical assessment scales and biomarkers). In addition, we initiated a collaboration with the USC Laboratory of Neuro Imaging (LONI) and Global Alzheimer's Association Interactive Network (GAAIN) on an image analysis pipeline developed by LONI, to develop a multimodal harmonized neuroimage analysis tool. The tool will be leveraged for automated quantification of MRI- and PET-derived biomarkers for use in disease progression modeling. Finally, we will integrate various modeling and analytical approaches to develop a clinical trial simulation tool.

Conclusions: The precompetitive infrastructure that CPAD provides is imperative to stakeholders sharing information and data, as well as for transforming these into actionable tools and solutions that address specific unmet needs in the drug development process. Through formal submissions for regulatory review and potential endorsement of solutions, CPAD can build consensus among experts and stakeholders and provide confidence to sponsors for the adoption of the tools.

DEEP LEARNING APPLICATION IN RETINAL IMAGING CLASSIFICATION OF ALZHEIMER'S DISEASE. Dumitrascu OM, Zhu W, Qiu P, Nandakumar K, Wang Y. Mayo Clinic Arizona; Arizona State University; Washington University.

Background: Alzheimer's Disease (AD) has increasing prevalence with vast societal and public health implications. There is a critical unmet need to develop biomarkers for early AD diagnosis. Recent scientific advances underscore retinal vascular changes and retinal abnormal protein deposition mirroring the changes in the AD brain. We have previously shown that retinal vascular tortuosity correlate with neurocognitive dysfunction and may predict AD. Retinal fundus photography is a cost-effective and high-resolution imaging tool to study retinal vascular changes in AD and emerge as a noninvasive biomarker for early AD diagnosis and monitoring. Handcrafted identification of the retinal vascular features on color fundus images is laborious, subjective, and prone to bias. Hence, developing automated retinal imaging tools has attracted strong research interest. Here, we leverage deep neural networks to develop an automatic framework to classify AD and extract AD retinal fundus imaging biomarkers using weakly supervised localization and Gradient-weighted Class Activation Mapping.

Methods: Our proposed framework is a two-stage system informed by previous research supporting retinal vascular dysfunction in AD. We used non-mydratic color retinal fundus images from AD patients from Mayo Clinic and cognitively normal controls (NC) from the Eyepacs database. In the first stage, a U-Net based network was applied to raw macula-centered and optic-disc-centered fundus images to produce vascular segmentation. The obtained binary vessel segmentation was subsequently fed into the encoder of the U-Net for feature extraction. The feature extractor is initialized with the weights from the first stage, since the contextual features from the U-Net encoder is useful for classification. The extracted features were fed to an average pooling layer and a fully connected layer with a Softmax activation to output probabilistic prediction.

Results: The U-Net is pretrained on the Digital Retinal Images for Vessel Extraction (DRIVE) dataset. We selected one image with the best segmentation from each subject, which resulted in 40 training images and 16 testing images. The problem is formulated as a binary classification task with positive class (AD) and negative class (NC). Our trained model achieved an area under ROC curve (AUC-ROC) of 0.938 on the testing set. The generated 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 optic head are highlighted in NC. Overall, our proposed network identifies retinal blood vessel branches with tortuosity change as potential identifier of AD.

Conclusions: We present a novel retinal imaging-based deep learning analysis framework for AD screening. Our preliminary results in a small data set demonstrated the feasibility of our DL model and a strong promise to identify automated retinal imaging biomarkers for AD diagnosis. Future research will include larger datasets of AD and preclinical AD subjects.

DEMENTIA-RELATED ANXIETY: WHAT'S THE WORRY? Maxfield M, Peckham A, James D.
Arizona State University; University of South Alabama; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease and related dementias (ARD) are prevalent, without cures, and contribute to declining functional independence and increasing neuropsychiatric symptoms. Their widespread effects make managing ARD financially, socially, and psychologically difficult, and the associated symptoms present challenges for the diagnosed individual as well as their family, friends, and caregivers. These features represent at least some of the reasons ARDs are feared diagnoses. Dementia-related anxiety (DRA) is anxiety about a current or potential ARD diagnosis. From the perspective of self-determination theory (Ryan & Deci, 2017), it is possible that DRA develops, at least partly in response to anticipation that ARD symptoms will undermine the three core psychological needs of autonomy, competence, and relatedness.

Methods: The data presented here are part of a larger mixed methods study; data collection occurred between November 2018 and June 2019. Relying on qualitative semi-structured interviews, participants were asked about their thoughts, feelings, and reactions regarding ARD, including anticipated responses to an imagined ARD diagnosis. A total of 50 participant interviews were transcribed verbatim. We took an inductive iterative thematic approach to data analysis. Initially, to enhance trustworthiness, four researchers independently reviewed five transcripts asking the data 'what seems to make people worry about dementia' while keeping in mind 'people express worry/anxiety/concern differently' and met to discuss potential trends and areas of focus. Through this process, we developed a codebook, and all transcripts were coded by two researchers. Once transcripts were coded, codes were reviewed by three researchers simultaneously to assess adequacy and identify subthemes. Relying on this iterative process, we adopted and revised themes as more responses and codes were reviewed.

Results: The thematic analysis revealed three core factors that contribute to anxiety about ARD and may compromise one's sense of autonomy, competence, and relatedness. Participants described a 'fear of becoming a burden' to family and friends as a result of advancing ARD symptoms, a fear of 'losing oneself' in which they discussed a fear that progressive symptoms would undermine one's core identity and relationships, and a fear of losing control and independence as a result of advancing ARD symptoms. Participants also noted various coping strategies they anticipate using to manage the fear of a potential ARD diagnosis and the associated symptoms, such as making plans for later stages in life (e.g., identifying a power of attorney, making funeral arrangements), feeling supported by family and friends, using strategies to manage current memory challenges, normalizing age-related cognitive changes, and accepting that ARD that disappointments, including ARD diagnoses, are simply a part of life.

Conclusions: The current research offers insight into factors that contribute to and help reduce DRA. The present findings advance understanding of the factors that drive DRA, which is an important first step to identify applicable, clinically relevant, and appropriate interventions and supports to meet the needs of older adults experiencing DRA.

DIETARY CHOLINE DEFICIENCY THROUGHOUT ADULTHOOD INDUCES SYSTEMS-WIDE DYSFUNCTION AND INCREASES ALZHEIMER'S DISEASE RISK ACROSS SEVERAL PATHOGENIC AXES. Judd JM, Dave N, Decker A, Winslow W, Sarette P, Espinosa OV, Sandler J, Bilal A, Tallino S, McDonough I, Winstone JK, Blackwood EA, Glembotski C, Karr T, Velazquez R. Arizona State University; University of Arizona College of Medicine–Phoenix; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is a widespread and costly health burden, creating an urgent need for insight into modifiable environmental risk factors, such as diet, to reduce disease incidence. The B-like vitamin choline plays key roles in healthy body and brain function. While some choline is produced endogenously by the phosphatidylethanolamine N-methyltransferase (PEMT) enzyme in the liver, these quantities are insufficient for healthy metabolic function, necessitating dietary intake. While choline supplementation above the adequate daily intake (ADI) has been shown to reduce AD pathology, the role of choline deficiency on AD has not been investigated. Given that recent reports estimate ~90% of Americans do not reach ADI of dietary choline, it is imperative to determine whether dietary deficiency increases disease outcomes.

Methods: Here, we placed 3xTg-AD mice, a model of AD, and non-transgenic (NonTg) control mice on either an adequate choline (ChN) or choline deficient (Ch-) diet from 3 to 12 months of age (early to late adulthood). Mice were behaviorally tested on the rotarod task and Morris water maze at 10 months of age to assess motor function and spatial learning and memory, respectively. To determine whether Ch- impairs glucose metabolism, we performed a glucose tolerance test (GTT). Mice were euthanized and blood, liver, heart and brain tissue were collected for biochemical and neuropathological analysis.

Results: Ch- drastically reduced plasma choline and acetylcholine levels, promoted weight gain, and impaired both motor function and glucose metabolism in both genotypes, with 3xTg-AD mice showing greater deficits. Tissue analyses showed cardiac and liver pathology in all Ch- mice, with the greatest severity in 3xTg-AD Ch- group. Analysis of brain tissue revealed elevated levels of soluble and insoluble fractions of Amyloid- β (A β) 40 and 42, in addition to soluble A β oligomers in 3xTg-AD Ch- mice. Soluble levels of phosphorylated tau (ptau) at serine (ser) 181 and 396, and insoluble ptau at ser181 were significantly elevated in 3xTg-AD Ch- mice. Unbiased stereology showed a higher number of AT8-(ser 202/threonine 205) positive cells in CA1 of the hippocampus of 3xTg-AD Ch- mice. To gain mechanistic insight, we performed unbiased proteomics of hippocampal and blood plasma samples. Ch- altered hippocampal networks associated with microtubule function, protein transport, and postsynaptic membrane regulation. In plasma, Ch- altered networks associated with insulin metabolism, mitochondrial function, and inflammation.

Conclusions: Collectively, these data highlight the importance of adequate dietary choline intake throughout adulthood and suggest that dietary choline deficiency induces system-wide dysfunction and increases the risk of AD across several pathogenic axes.

EARLY-STAGE PARTNERS IN CARE (EPIC) LIVING ALONE: A VIRTUAL PILOT FOR PEOPLE LIVING ALONE WITH EARLY-STAGE MEMORY PROBLEMS. Glinka A, Gonzalez-Pyles S, Carll P, Perez, S, Coon DW. Arizona State University; Arizona Alzheimer's Consortium.

Background: In 2022, 6.5 million people are living with Alzheimer's disease (AD) in the United States, 26% of them live alone. 85% of people diagnosed with Alzheimer's disease and related dementias (ADRD) want to be at home for as long as possible. People living alone are less likely to receive a correct dementia diagnosis and to recognize their own limitations. Moreover, no evidence-based interventions have been identified to help people with ADRD who live alone manage their ongoing memory changes, associated stressors and related distress, and prepare for the future. As our society continues to age, older adults living alone with memory challenges and their providers need evidence-based interventions to address the needs and concerns of this older population.

Methods: Using feedback back from five focus groups with 26 older adults facing cognitive changes as they aged (38% who lived alone), we adapted an evidence-based intervention EPIC (Early-stage Partners in Care) to focus on people living alone (EPIC Living Alone) with early-stage memory problems. EPIC Living Alone is a feasibility and acceptability pilot study involving a 7-week skill-development and future care planning intervention program conducted over Zoom. It consists of 6 weekly group sessions lasting 2.5 hours each and 1 individualized 90-minute session. EPIC Living Alone creates a supportive environment that provides education on memory changes associated with dementia; develops mood management, communication, and stress reduction skills; helps clarify care values and preferences for future care tasks; and develops an individualized plan for the future. Participants completed individual assessments via Zoom with trained staff using measures with established reliability and validity.

Results: In this initial pilot, seven participants completed all seven sessions and the project's assessments supporting both feasibility and acceptability. Forty-three percent (43%) of participants were male and 71% lived outside the state of Arizona spanning from Hawaii to Massachusetts. Their ages ranged from 60 to 87 years (mean=71.4, SD=9.5) and 43% had a diagnosis of Alzheimer's Disease. Post-intervention perception of benefit and satisfaction survey responses indicate that early-stage participants living alone benefited overall from the intervention. Participants reported EPIC Living Alone helped them better understand memory loss and its effects (100%); make them feel more confident in dealing with problems related to memory loss (100%); made their life easier (100%); and better prepared to take care of their future care needs (100%). Participants also reported their emotional well-being had improved (86%) and their communication skills had improved (86%). Participants stated they felt "less alone" and better able to relate with others who were in a similar situation. Moreover, participants felt the individualized session was very "powerful" in helping them understand their preferences for future care and be better prepared to handle future care needs.

Conclusions: Findings from this initial pilot of EPIC Living Alone were very promising and indicated that participants benefitted in multiple ways including feeling better prepared for the future. A 100% retention rate combined with these positive perceptions of benefit support the development of a larger clinical trial to evaluate participant outcomes (e.g., depressive symptoms, overall stress, and other quality of life indicators).

EFFECTS OF MINDFUL AWARENESS PRACTICE (MAP) INTERVENTION ON SUBCLINICAL DEPRESSIVE AND ANXIETY SYMPTOMS AND GENERAL COGNITIVE FUNCTION IN OLDER ADULTS WITH MILD COGNITIVE IMPAIRMENT: A 5-YEAR FOLLOW-UP OF THE MAP-RANDOMIZED CONTROLLED TRIAL. Ng TKS, Tan XR, Chen ACC, Lei F, Lu Y, Yu F, Kua EH, Mahendran R. Arizona State University; National University of Singapore; Singapore Institute of Technology; Shandong University; National University Hospital, Singapore; Arizona Alzheimer's Consortium.

Background: Few randomized controlled trials (RCTs) investigated the effects of mindfulness intervention on affective and cognitive symptoms in older adults with mild cognitive impairment (MCI). Furthermore, no RCTs on mindfulness followed participants beyond two years. We aimed to examine the longitudinal effects of a mindful awareness practice (MAP) intervention on depressive, anxiety, and cognitive symptoms in MCI.

Methods: In this parallel-arm and assessor-blinded RCT, 55 community-dwelling older adults with MCI were randomized into the MAP or active control, i.e., health education program (HEP). Intervention sessions were conducted weekly for three months and monthly for the subsequent six months. Assessments and follow-up were conducted at baseline, 3-month, 9-month, and 5-year time-points. Depressive, anxiety, and cognitive symptoms were measured using the Geriatric Depression Scale-15 (GDS-15), Geriatric Anxiety Inventory-20 (GAI-20), and Mini-Mental State Exam (MMSE), respectively. Linear-mixed models, following the intention-to-treat principle, were used for data analyses.

Results: A total of 55 participants aged 60 to 86 (Mean age: 71.3 ± 6 years old) was recruited, with $n=28$ allocated to the MAP arm and $n=27$ allocated to the HEP arm. Compared to HEP, GDS-15, GAI-20, and MMSE scores did not differ significantly in MAP during follow-ups.

Conclusions: Compared to HEP, MAP did not improve affective symptoms nor delay deteriorations in general cognitive function in community-dwelling older adults with MCI. Compared to our previous findings showing domain-specific improvements in MAP over HEP in attention and memory up to 9-month, this study highlights the importance of examining domain-specificity using detailed cognitive measures in non-pharmacological intervention with MCI.

EXAMINING THE CELLULAR DISTRIBUTION OF TELOMERE PROTEIN RAP1 DURING OXIDATIVE STRESS. Whetzel A, Bandara D, Lewis KN, Swanson MJ, Bae NS. Midwestern University; Arizona Alzheimer's Consortium.

Background: Telomeres are nucleoprotein structures at the ends of linear chromosomes. In mammals, a six-member protein complex, called shelterin, protects telomeres from being recognized as DNA double-strand breaks and from nucleolytic degradation. Of the six proteins, RAP1 (for Repressor/Activator Protein 1) is a key protein that represses homology-directed repair and protects telomeres from non-homologous end joining, thus maintaining genome stability. RAP1 is recruited to telomeres by the shelterin subunit, TRF2, which binds DNA directly. Mammalian RAP1 also has roles beyond the nucleus. Recently, RAP1 was shown to form a complex with IKB kinases and directing them to phosphorylate the p65 subunit of NF- κ B in the cytoplasm. The NF- κ B signaling pathway plays an important role in the immune system by regulating the expression of cytokines and immunity involved receptors. Among the stimuli that activate the NF- κ B pathway is the accumulation of reactive oxygen species (ROS). ROS can be introduced exogenously, but ROSs are also generated and accumulate naturally in tissues as cells undergo replication, i.e., as they age.

Methods: The glioblastoma cell line U251 and neuroblastoma cell line SH-SY5Y were used. To investigate the localization of RAP1 from the nucleus to the cytoplasm, we induced oxidative stress to cells using H₂O₂ treatment or nutritional deprivation. To study the relationship between the phosphorylation state of RAP1 and RAP1 localization, phosphor mutants were transfected. The transfection efficiency was tested by verifying the expression level using immunoblotting. Cellular extracts were fractionated into nuclear and cytoplasmic portions to measure the levels of the different RAP1 constructs in each of the cellular compartments to determine the effect of RAP1 on normal localization. Fluorescence microscopy will be used to confirm the immunoblotting data.

Results: When cells were under oxidative stress, RAP1 was re-distributed from the nucleus to the cytoplasm. Regarding the phosphorylation state of RAP1, RAP1 is localized to the nuclear membrane when RAP1 cannot be phosphorylated.

Conclusions: We were able to show that when cells age, a critical component of the telomere that is responsible for protecting the integrity of the genome is re-localized to the cytoplasm, and that the phosphorylation state of RAP1 aids in its re-localization.

EXERCISE TRAINING PREVENTS THE LOSS OF WALL THICKNESS AND LOWERS EXPRESSION OF ALZHEIMER'S RELATED PROTEINS IN 3XTG MOUSE JEJUNUM. Al-Nakkash L, Mason D, Ismail N, Bowman T, Ahlert J, Rubin M, Smith E, Rosander A, Broderick TL. Midwestern University; Arizona Alzheimer's Consortium.

Background: Aging and neurodegenerative diseases including Alzheimer's Disease (AD) have been associated with reduced intestinal motility and constipation. Moreover, amyloid beta deposition associated with AD, has also been detected within the enteric nervous system and is associated with decreased intestinal motility. Exercise training plays an important role in the treatment of AD, however its effects on AD intestinal tissue is unknown. The goal of this study was to assess changes in intestinal structure of 3xTg-AD mice and determine the impact of exercise.

Methods: Triple transgenic 3xTg-AD male mice were used (aged 8-weeks at the start of study). These mice have 3 mutant genes (Ab, presenilin-1, and tau), which parallels human AD. Mice were assigned to one of the following groups for the 5-month study duration: 3xTg-AD control (AD), and 3xTg-AD mice exercise trained (AD+Ex). Exercised mice were subjected to treadmill running 5 days/week for 5-months. Wild type (WT) mice served as the controls. At the completion of the study, segments of jejunum were isolated and stored at -80°C for western blot, or sectioning and staining.

Results: Histomorphometry studies indicated that jejunum total wall thickness was significantly decreased in the AD mice compared to WT. Villi length, crypt depth and collagen content (trichrome staining) were increased in AD mice versus WT controls. Expression of smooth muscle actin in jejunum was also decreased in AD mice. Exercise prevented these changes. Total protein expression of cyclin dependent kinase 5 (CDK5) involved in neural cell death and hyperphosphorylation of tau and Caspase 3 (an apoptotic marker) were significantly increased in AD compared to WT and exercise prevented these AD-mediated increases.

Conclusions: The beneficial effects of exercise in this AD model were noted with the mitigation of collagen deposition, wall thickness, and AD-related protein expression. These data suggest that habitual exercise in the 3xTg-AD mouse model provides benefits on gastrointestinal health.

Support: Midwestern-Arizona Alzheimer's Consortium.

GLYCOSYLATED HORMONES AS BRAIN-PENETRANT NEUROPROTECTIVE DRUGS. Polt R, Falk T, Streicher J, Heien ML, Apostol CR, Szabo L, Alabsi W, Tanguturi P. University of Arizona; Arizona Alzheimer's Consortium.

Background: Studies with O-linked glycopeptide drug candidates suggest that two conformational ensembles exist— A highly flexible group of water soluble structures (random coils), and a much smaller set of “amphipathic states” that are more constrained, and membrane-bound. Most if not all endogenous neuropeptides possess strong amphipathic character that constrain them to membrane surfaces. Pioneering studies with enkephalins, endorphin/dynorphin analogues, and PACAP/VIP agonists suggest that the modulation of membrane affinity by glycosylation (or the introduction of other water-soluble moieties) produces “biosian glycopeptides” that are systemically available (favorable PK/PD), and can cross the BBB.

Methods: The pituitary hormone PACAP has been glycosylated to produce a number of agonists for the receptors PAC1, VPAC1 and VPAC2. Truncation of the peptide chain and minimal substitution of critical amino acids has produced brain-penetrant analogues selective for PAC1 and VPAC2. PAC1 activation is neuroprotective centrally, likely due to M2 vs M1 activation of microglia, and VPAC1 activation peripherally is likely to increase blood flow to brain tissue.

Results: Peripheral (ip) administration of PACAP-lactosides and/or PACAP-melibiosides showed potent effects on chemically-induced Parkinsonism in rats. Other animal models (mice) for mild TBI and Stroke also showed a potential for the treatment of these brain injuries.

Conclusions: Glycosylated PACAP analogues are more stable and brain-penetrant, and show great promise for the treatment of CNS injuries, and may be useful in slowing or preventing neurodegeneration.

IMPROVED PREDICTION OF THE MEASUREMENTS OF TAU AND BETA-AMYLOID BURDEN USING HIPPOCAMPAL SURFACE MULTIVARIATE MORPHOMETRY STATISTICS AND SPARSE. Wu J, Zhu W, Gui J, Lepore N, Reiman EM, Caselli RJ, Thompson PM, Chen K, Su Y, Wang Y. Arizona State University; Banner Alzheimer's Institute; University of Arizona; School of Cyber Science and Engineering Southeast University; Children's Hospital Los Angeles; Mayo Clinic Arizona; University of Southern California; Arizona Alzheimer's Consortium.

Background: Tau protein tangles and Beta-Amyloid ($A\beta$) plaques in the brain are now widely recognized as the defining hallmarks of Alzheimer's disease (AD), followed by structural atrophy detectable on brain MRI scans. However, current methods to detect tau/ $A\beta$ pathology are either invasive (lumbar puncture) or quite costly and not widely available. In our previous work, structural MRI-based hippocampal multivariate morphometry statistics (MMS) showed superior performance as effective neurodegenerative biomarkers for preclinical AD and Patch Analysis-based Surface Correntropy-induced Sparse coding and max-pooling (PASCs-MP) has excellent ability to generate low-dimensional representations with strong statistical power for brain amyloid prediction. In this work, we apply these to predict Tau deposition in Braak12 and Braak34 brain regions and the measurement of amyloid, Centiloid

Methods: Firstly, hippocampal structures are segmented from registered brain MR images with FIRST from FSL. Hippocampal surface meshes are constructed with marching cubes algorithm. Secondly, the surfaces are parameterized with the holomorphic flow segmentation method. After the surface fluid registration, the hippocampal MMS features are calculated at each surface point. We use a PASCs-MP and regression system to refine and predict Braak12, Braak34 and Centiloid. We randomly select patches on each hippocampal surface and generate a sparse code for each patch with our PASCs mode and adopt max-pooling operations on the sparse codes to generate a new representation (a vector) for each subject. Finally, ridge regression models are trained to predict the tau measures. The prediction models are validated with a 10-fold cross-validation scheme for ten times and the average root mean squared error (RMSE) is used for measuring the results. Besides, we also leverage the Pearson correlation analysis to evaluate the relations between real Tau measures and predicted ones

Results: From the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu), we identified 925 subjects for tau deposition and 1127 for $A\beta$. The RMSEs to predict Braak12 are 0.456, 0.455, 0.406 and 0.367 for these four biomarkers, hippocampal surface area, hippocampal volume, SPHARM and our MMS-based PASCs-MP representation. The RMSEs to predict Braak34 are 0.456, 0.455, 0.431 and 0.410 and the ones to predict Centiloid are 41.05, 41.08, 40.69 and 30.8. Our PASCs-MP always has the minimum RMSEs in predicting the measurements for tau/ $A\beta$.

Conclusions: MMS-based PASCs-MP representations achieve superior performance in predicting the tau and $A\beta$ deposition. In the future, we will use this framework to study other AD-related regions of interest and further improve the framework to visualize the disease-related features on the surface.

INCREASED SPATIAL EXTENT OF CEREBRAL TAU PET ELEVATIONS IN FORMER NFL AND COLLEGE FOOTBALL PLAYERS FROM THE DIAGNOSE CTE RESEARCH PROJECT.

Chen K, Reiman EM, Luo J, Protas H, Cummings JL, Shenton ME, Stern RA, Su Y for the DIAGNOSE CTE Research Project. Banner Alzheimer's Institute; Arizona State University; University of Arizona; Translational Genomics Research Institute; Boston University School of Medicine; Brigham and Women's Hospital; University of Nevada; Arizona Alzheimer's Consortium.

Background: We previously found greater spatial extent of flortaucipir (tau) PET elevations in Arizona-Boston (DETECT) Study of 26 former National Football League (NFL) players than in 31 normal controls—using a voxel-based Majority Count Statistics (MCS) algorithm which enabled us to detect tau PET abnormalities in the player group free from the inflated Type 1 error associated with voxel-wise multiple comparisons (Stern et al, NEJM 2019). We now confirm this finding in a larger group of former NFL players, former college football players and asymptomatic controls without exposure to repetitive head impacts from the DIAGNOSE CTE Research Project.

Methods: Flortaucipir PET images were acquired in 106 former NFL players, 51 former college players, and 53 unexposed controls, 57.71±8.37 years of age. An automated algorithm (SPM12) and co-registered MRIs were used to spatially normalize PET images into Montreal Neurological Institute template, and compute statistical brain maps of group differences in regional cerebral-to-cerebellar crus1 standard uptake value ratio (SUVR), controlling for the participants' age and race with $P \leq 0.005$, uncorrected for multiple comparisons. Our MCS was then applied with 1,000 iterations to test the hypothesis that there would be a greater number of cerebral voxels with SUVR elevations in each and combined player group versus control group, as well as between the NFL versus college player groups.

Results: As predicted, the NFL, college player and aggregate player groups each had significantly more cerebral voxels with flortaucipir SUVR elevations than in the control group (postulated vs opposite directions: 53,879 vs 79, 79,552 vs 89 and 100,837 vs 86 voxels), respectively, MCS $P < 0.001$, but not between former NFL and former college players (482 versus 306, $p = 0.305$).

Conclusions: Using a voxel based MCS analysis, former NFL and college football players have a greater spatial extent of elevations in tau PET measurements than asymptomatic controls. Additional work is needed to clarify the biological nature of these small but spatially extensive elevations, the extent to which they are related to symptom severity, cognitive performance, repetitive head impact exposure, and other risk or resilience factors, and the extent to which they are associated with subsequent clinical decline.

INVESTIGATING BIOLOGICAL PATHWAYS UNDERPINNING THE LONGITUDINAL ASSOCIATION BETWEEN LONELINESS AND COGNITIVE IMPAIRMENT. Yu K, Ng TKS. University of Southern California; Arizona State University; National University of Singapore; Arizona Alzheimer's Consortium.

Background: Neurofibrillary tau pathology spread in Alzheimer's disease (AD) mostly shows a stereotypical pattern of topographical progression previously described as the Braak staging system. However, both Loneliness precedes the onset of cognitive impairment (CI) in older adults. Although the mechanisms through which loneliness "gets under the skin" to influence the risk of developing CI has been conceptually proposed, they are rarely empirically examined. The Evolutionary Theory of Loneliness posits that loneliness as a stressor could cause dysregulations in multiple physiological systems. The current study investigated whether inflammatory, cardiovascular, and kidney biomarkers mediate the longitudinal association between loneliness and CI.

Methods: Cross-lagged panel models (CLPM) were used to examine the hypothesized relationships, using 2006, 2010, and 2014 waves of data from the Health and Retirement Study (N=7,037). Loneliness was measured with the 3-item UCLA loneliness scale. CI was assessed with the modified telephone interview for cognitive status. Biomarkers included HbA1C, LDL cholesterol, HDL cholesterol, CRP, and Cystatin C. Using a stepwise model, first, the model included only loneliness, CI, and biomarker variables; then, sociodemographic covariates were added; lastly, health and behavioral covariates were controlled for.

Results: In unadjusted and partially adjusted models, loneliness was associated with higher odds of worse cognitive status in an 8-year follow-up. Only HbA1C mediated the longitudinal association between loneliness and CI. However, after further controlling for health status, all associations became non-significant.

Conclusions: Examining a large number of participants and linking a limited number of biological markers with cognition and loneliness longitudinally, our empirical data did not support theoretical propositions, highlighting the critical importance of controlling for confounders in future studies examining longitudinal mediational relationships underlying loneliness and CI.

INVESTIGATING THE EFFECT OF TAU DEPOSITION AND APOE ON HIPPOCAMPAL MORPHOMETRY IN ALZHEIMER'S DISEASE: A FEDERATED CHOW TEST MODEL. Wu J, Su Y, Reiman EM, Caselli RJ, Chen K, Thompson PM, Wang J, Wang Y. Arizona State University; Banner Alzheimer's Institute; University of Arizona; Mayo Clinic, Scottsdale; University of Southern California; Arizona Alzheimer's Consortium.

Background: Tau tangle is the specific protein pathological hallmark of Alzheimer's disease and plays a crucial role in leading to dementia-related structural deformations observed in MRI scans. The volume loss of hippocampus is mainly related to the development of AD. Besides, APOE also has significant effects on the risk of developing AD. However, few studies focus on integrating genotypes, MRI, and tau deposition to infer multimodal relationships. In this paper, we proposed a federated chow test model to study the synergistic effects of APOE and tau on hippocampal morphometry.

Methods: The image-tau relationship (correlation) is diluted when the population is mixed, but when we stratify the population based on their genotypes, we can observe strong correlations across subgroups. Therefore, the samples are first stratified into three cohorts according to their APOE genotypes and each imaging biomarker is used as the predictor, and the tau measure (Braak34) is used as the response in each group. Then, a p-value is computed with the federated chow test model to evaluate the difference in these cohorts. In this work, the hippocampal structures are segmented from registered brain MR images and smoothed hippocampal surfaces are then generated. The hippocampal volumes are first used as the image biomarker. After the surface parameterization and fluid registration, the hippocampal radial distance (RD) and tensor-based morphometry (TBM) features are calculated at each surface point, which are used as the image biomarkers.

Results: We first adopt the hippocampal volume as the imaging biomarker in our model and p-values are significant for both side hippocampus. Then, we apply two morphometry features, radial distance and surface tensor-based morphometry, as the imaging biomarker to figure out the regions where the atrophy focuses. The average p-values for each RD and TBM on each surface are all significant. The atrophy focuses on cornu ammonis 1 (CA1 subfield) and subiculum.

Conclusions: In this paper, we proposed a federated model to investigate the effect of tau deposition and APOE on hippocampal morphometry in AD. In the future, we will use this model to study A β and AD-related SNP, like rs11136000 on CLU.

ISCHEMIC OUTCOME IN YOUNG AND ADULT MALE AND FEMALE OFFSPRING AFTER MATERNAL DEFICIENCIES IN ONE-CARBON METABOLITES DURING PREGNANCY AND LACTATION. Clementson M, Hurley L, Jauhal J, Coonrod S, Bennett C, Pull K, Pascual A, Wasek B, Bottiglieri T, Malysheva O, Caudill MA, Jadavji NM. Midwestern University; Baylor Scott & White Research Institute; Cornell University; Carleton University; Arizona Alzheimer's Consortium.

Background: Maternal one-carbon metabolism, including dietary levels of folic acid and choline, play an important role in early life programming. There is a well-established connection between the fetal environment and the health status of offspring. However, there is a gap in knowledge on how maternal nutrition will affect the health status of the offspring after a cardiovascular event like ischemic stroke. The aim of our study was to investigate the role of maternal dietary deficiencies in folic acid or choline on stroke outcome in 3- and 10-month-old male and female offspring. We hypothesize that maternal dietary deficiencies of folic acid or choline will impact early life programming of the fetus, and therefore lead to worse health outcomes after ischemic stroke in early adulthood.

Methods: Adult female mice were fed a folic acid deficient diet (FADD), a choline deficient diet (ChDD), or a control diet (CD) four weeks prior to pregnancy to deplete stores, they were continued on diets during pregnancy and lactation. Male and female offspring were weaned onto a control diet and at 2 or 10 months of age were subject to ischemic stroke within the sensorimotor cortex via the photothrombosis ischemic damage model. At 3 or 11 months of age, motor function was measured in offspring and tissue was collected for analysis.

Results: Mothers maintained on either a FADD or ChDD had reduced levels of S-adenosylmethionine in liver tissue compared to controls. In offspring after ischemic stroke, motor function was impaired in 3-month-old male and female offspring from deficient mothers compared to control diet offspring. In 11-month-old mice there was no impact of maternal diet on motor function, but we observed sex differences. Male middle-aged adult mice had worse motor function compared to female offspring. In brain tissue, there was no impact of maternal diet on ischemic damage volume in 3-month-old animals. Interestingly, maternal diet impacted 10-month-old male and female offspring. Neurodegeneration and choline metabolism in ischemic brain tissue was also impacted in 3 and 11-month-old offspring.

Conclusions: The findings of our study suggest that a maternal diet deficient in either choline or folic acid impacts stroke outcome in young animals compared to middle-aged animals. This result points to the important role of the maternal diet in early life programming, while emphasizing its effects on both fetal development and long-term cerebrovascular health.

MICROBIAL AND PROTEOMIC ANALYSES REVEALED SIGNIFICANT CHANGES IN MICROBIOME COMPOSITION AND DEFENSE RESPONSE IN ALZHEIMER'S GUT. Mastroeni D, Krajmalnik-Brown R, Cheng Q, Karr T. Arizona State University; Arizona Alzheimer's Consortium.

Background: Gut microbiota can influence physiological aspects of the human body, including direct communication with the brain. The gut has approximately 500 million nerve cells that regulate a host of brain processes. By now, the idea that gut microbiota affects a person's health is not revolutionary. It is known that these microbes influence a multitude of cellular processes and neurological conditions, like anxiety, Parkinson's, and autism spectrum disorders. Scientists have known for some time that the gut microbiota plays a critical role in the production and biodegradation of neurotransmitters such as acetylcholine, a critical co-factor in Alzheimer's Disease (AD). This relationship between microbes and human health from an evolutionary perspective is unquestionable, but factors that can alter the symbiotic relationship between the host and its microbes remain to be uncovered.

Methods: Microbial Analysis: Gut microbial community sequencing and analysis (Dr. Krajmalnik-Brown and Dr. Cheng): Extract DNA from the transverse colon of 25 clinically and pathologically confirmed AD cases and 25 matched controls (e.g., sex, PMI, ApoE status, age, etc.). Perform 16S rRNA gene amplicon sequencing. We analyzed sequenced raw reads and explored microbial community composition using the Quantitative Insights into Microbial Ecology (QIIME 2, v2021.2) platform. We assess the gut microbial diversity using the R packages phyloseq (v1.34.0) and vegan (v2.5-7). We used Linear discriminant analysis Effect Size and R package DESeq2 to identify microbes that are significantly different between AD patients and matched controls. LC-MS of Transverse Colon: Total protein from the same samples which we used for Gut microbial community sequencing and analysis were resuspended in 8M urea and digested overnight with endopeptidase LysC and trypsin at a 1:10 protease: substrate ratio as per ASU Mass Spec Core SOP. The resulting peptides are, de-salted, dried down, and dissolved in 40ul of 0.1% (v/v) formic acid, were loaded onto a 25-cm EasySpray HPLC column, and eluted over a 2-h gradient (Buffer A 0.1% (v/v) formic acid in water, buffer B, 0.1% (v/v) formic acid in acetonitrile, final 50% B) using an UltiMate 3000 RSLCnano system. Peptides were eluted via nano-ESI source at 2.4-kV and analyzed on an Orbitrap Fusion Lumos mass spectrometer. High-resolution data-dependent acquisition of MS1 spectra was collected at 120,000 resolution (FWHM), and MS2 spectra analyzed in the Orbitrap at 15,000 resolution (FWHM) following higher energy dissociation (HCD) and/or electron-transfer dissociation (ETD).

Results: We analyzed the bacterial communities present in the transverse colon of 54 AD and normal control patients from the Banner Sun Health Brain Bank. Our results indicate that bacterial communities in the gut of AD patients were significantly different from those in the gut of controls. Taxa belonging to several genera including Fusobacterium and Bacteroides had significantly higher relative abundances in AD patients compared to controls ($p < .05$). In matching subjects, we analyzed the gut tissue proteome using LC-MS/MS. We have identified several novel biological pathways that are downregulated in AD gut samples. One of the most significant downregulated biological pathways was the defense response to bacteria. This novel finding is directly linked to the inability to clear potential threats and the inability to trigger a humoral response in the presence of noxious pathogens. As such, subsequent analysis showed a significant down-regulation of complement genes in AD gut compared to control ($p < .006$).

Conclusions: The fact that greater than twenty proteins within the defense response to bacteria pathway are downregulated in the AD gut indicates a failing complement system. The inability to detect threats could lead to the activation of latent microbes or increase the number of harmful bugs altering the symbiotic relationship between the host and its microbes. We are in the process of analyzing microbial proteomes and will integrate microbial community composition results with proteomics to identify AD markers and explore potential microbial mechanisms.

MICROSTRUCTURAL MR MARKERS OF ALZHEIMER'S DISEASE PATHOLOGY IN POST-MORTEM HUMAN TEMPORAL LOBE. Comrie CJ, Dieckhaus LA, Beach TG, Serrano GE, Hutchinson EB. University of Arizona; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Alzheimer's Disease (AD) is an irreversible degenerative brain disease affecting 5.5 million Americans. However, clinical markers for early diagnosis are lacking and approximately 20% of all AD cases are ultimately misdiagnosed. Current clinical MRI is capable of reporting severe brain atrophy, but fails to recognize earlier biomarkers associated with more subtle cellular and molecular changes. Microstructural Magnetic Resonance Imaging (MRI) techniques are promising to address this challenge and may sensitively detect and distinguish tissue degeneration, tauopathies, and beta amyloid plaques to improve accuracy of diagnosis and enable early detection. The objective of this study was to identify and compare the most promising microstructural markers of AD pathology over a range of diffusion-based (DTI, MAP-MRI and NODDI) and relaxometry-based (MWF and BPF) MRI methods by investigating post-mortem human temporal lobe specimens at high resolution and high image quality.

Methods: Fourteen post-mortem human temporal lobe samples were received from the Banner Sun Health Brain and Body Donation Program. Two temporal lobe samples of known pathologies, Braak stage 4 AD and healthy, were utilized in development of methods and comprehensive metric comparisons. The remaining twelve samples were imaged and analyzed for comparative analysis of metrics across specimens. All samples were prepared according to with short post-mortem interval, block fixation by paraformaldehyde and rehydration by storage in saline. Samples were prepared in 50 ml falcon tube and Fluorinert for scanning. Images were acquired at 250 micron isotropic resolution using a 7T Bruker Biospec MRI scanner, including multi-shell diffusion weighted imaging (DWI) 201 DWI volumes over $b=0-6,000$ s/mm², quantitative magnetization transfer selective inversion recovery (SIR) for T1 and BPF mapping, and multi-spin echo (MSE) with TE=6-200ms for T2 and MWF mapping. Total scan time was approximately 50-60 hours. Diffusion pre-processing and DTI and MAP-MRI calculations were performed using TORTOISE 3.2.0 to generate fractional anisotropy (FA), mean diffusivity (MD), and propagator anisotropy maps (PA) among others. Advanced relaxometry mapping algorithms were accomplished using the REMMI toolbox in MATLAB to generate included myelin water fraction (MWF), bound pool fraction (BPF), T1, and T2 mapping.

Results: Correlation analysis of 11 samples found a negative correlation of -0.68 was found between PA and Braak Score while no correlation was present for FA. This relationship was further explored through 1D histograms comparing healthy and AD samples where PA displayed specificity with a bimodal distribution and FA did not. In the TR, MSD, and MSK maps the correlations with Braak Score are as follows: 0.63, 0.66, and -0.71 respectively. RTOP had a negative correlation of -0.68 with Braak Score.

Conclusions: The most prominent results seen in this study were: 1) striking differences between DTI and MAP-MRI anisotropy metrics, 2) strong positive correlations with mean diffusivity, and 3) negative correlations regarding restricted or hindered water metrics. Anisotropy metric differences were clearly observed by correlation analysis and 1D histograms where a bimodal distribution is present for PA, but not FA, potentially corresponding to different tissue environments (e.g. axons vs. dendrites). This is also reflected in the correlation analysis where PA had a strong negative correlation, but FA lacked any correlation with the pathology present in the tissue. Correlations in diffusivity and restrictive metrics both indicate that the neurodegeneration present in the samples is the dominating trait. If any restriction is present due to increases in protein, then it is undetectable when strong neurodegeneration is also present.

MODERATING EFFECT OF COGNITIVE RESERVE ON BRAIN INTEGRITY AND COGNITIVE PERFORMANCE. Nelson ME, Veal BM, Andel R, Martinkova J, Veverova K, Horakova H, Nedelska Z, Laczó J, Vyhnalek M, Hort J. University of South Florida; Charles University and Motol University Hospital, Prague, Czech Republic; St. Anne's University Hospital Brno, Czech Republic.

Background: Dementia syndrome is one of the most devastating conditions in older adults. As treatments to stop neurodegeneration become available, accurate and timely diagnosis will increase in importance. One issue is that cognitive performance sometimes does not match the corresponding level of neuropathology, affecting diagnostic accuracy. Cognitive reserve (CR), which can preserve cognitive function despite underlying neuropathology, explains at least some variability in cognitive performance. We examined the influence of CR proxies (education and occupational position) on the relationship between hippocampal or gray matter volume and cognition.

Methods: We used data from the Czech Brain Aging Study. Participants were clinically confirmed to be without dementia (n=457, including subjective cognitive decline and amnesic mild cognitive impairment) or with dementia syndrome (n=113).

Results: For participants without dementia, higher education resulted in stronger associations between (a) hippocampal volume and executive control (b=0.09, p=.033), (b) total gray matter volume and language (b=0.12, p<.001), and (c) total gray matter volume and memory (b=0.08, p=.018). Similarly, higher occupational position magnified the association between total gray matter volume and (a) attention/working memory (b=0.09, p=.009), (b) language (b=0.13, p=.002), and (c) memory (b=0.10, p=.013). For participants with dementia, the associations between hippocampal (b=-0.26, p=.024) and total gray matter (b=-0.28, p=.024) volume and visuospatial skills decreased in magnitude with higher education.

Conclusions: The findings fit with past research in suggesting that cognitive reserve operates differently depending on whether participants have passed a clinical threshold. Specifically, higher reserve, especially more education, signals a stronger brain volume-cognition relationship prior to diagnosis but also a weaker relationship after diagnosis. We build on past research by including a comprehensive cognitive battery, two distinct diagnostic groups, and a sample from Central Europe.

MULTI-OMICS ANALYSIS SUGGESTS INCREASED EXOCYTIC PROCESSES IN THE BRAINS OF PATIENTS WITH TRISOMY-21 AND ALZHEIMER'S DISEASE. Piras IS, Beres S, Hudson S, Johnson M, Wright S, Tallino S, Head E, Huentelman M, Velazquez R. Translational Genomics Research Institute; University of California, Irvine; Arizona State University; Arizona Alzheimer's Consortium.

Background: Down syndrome (DS) affects one of every 700 births in the United States. By the age of 40, virtually all people with DS have sufficient A β deposits and tau tangles for a neuropathological diagnosis of Alzheimer's disease (AD). The epigenetic and transcriptomic changes that occur in key brain regions affected in people with DS and AD (DS-AD) remain elusive.

Methods: Here, we conducted a combined epigenomic/transcriptomic analysis on post-mortem brain samples from donors with AD (age: 86.7 ± 8.7 , M/F ratio: 1.1), DS-AD (age: 74.7 ± 16.7 ; M/F ratio: 1.2), and controls (CTL; age: 88.1 ± 3.8 ; M/F ratio: 0.8) across three brain regions: basal forebrain (BF), middle temporal visual area (MT) and middle frontal area (MF). DNA methylation was characterized with the Illumina MethylationEPIC array, whereas transcriptomic profiling was conducted using Illumina RNA-sequencing. After quality controls and normalization, we obtained a dataset of 190 samples, with expression and methylation values adjusted for confounding factors. Then, transcriptomic and methylation profiles were integrated using the Functional Epigenetic Module algorithm (FEM), which is capable of detecting groups of genes simultaneously differentially expressed and methylated that are located in the same protein-protein interaction (PPI) subnetwork.

Results: We applied the FEM algorithm after conducting differential expression and methylation analysis of all the pairwise comparisons between the groups (AD versus CTL; DS-AD versus CTL, and DS-AD versus AD) for all three brain regions, detecting significant results for the DS-AD versus CTL comparison in both BF and MF regions. In BF, we detected a PPI subnetwork including 83 genes, with ERGIC3 as the hub gene ($p = 0.01$). The network was enriched for gene ontology (GO) classes related to the activation in DS-AD of "SNARE binding" and "exocytic processes" (adj- $p > 4.2 \cdot 10^{-3}$). In MF, we detected two overlapping PPI networks with 19 genes each, including TRAPPC3 ($p = 0.024$) and TRAPPC9 ($p = 0.023$) as hub genes, mostly upregulated and enriched for "Rab GTPase binding" and "Golgi vesicle transport" (adj- $p > 1.3 \cdot 10^{-8}$).

Conclusions: These results seem to converge toward the activation of exosome secretion in the brains of patients with DS-AD, since SNARE and Rab GTPase proteins regulate the intracellular trafficking of endosomes and multivesicular bodies (MVBs) toward the plasma (PMID:27238186). Endosomal dysfunctions in neurons, observed in early DS and AD (PMID:9236226;10880397), are characterized by the accumulation of toxic materials in neuronal endosomes that can lead to neuronal vulnerability and degeneration (PMID:14982829). Interestingly, experimental evidence suggests that the enhanced exosome activity in DS, driven by CD63, might be a protective mechanism to decrease endosomal pathology (PMID: 28851452). We identified new key genes such as ERGIC3, TRAPPC3, and TRAPPC9 that can be investigated as potential targets to increase exosome activity to reduce neuronal vulnerability and degeneration in DS-AD.

NETWORK-BASED GENOME ANALYSIS OF COGNITIVE IMPAIRMENT IN A SOUTH AMERICAN INDIGENOUS POPULATION. Garcia AR, Lu YK, Gatz M, Mack WJ, Chui HC, Law M, Barisano G, Eid Rodriguez D, Gutierrez RQ, Copajira Adrian J, Bani Cuata J, Sutherland ML, Sutherland JD, Kraft TS, Borenstein AR, Irimia A, Thomas GS, Thompson RC, Miyamoto MI, Michalik DE, Wann LS, Walters EE, Allam A, Rowan CJ, Cummings DK, Highland HM, North KE, Finch CE, Stieglitz J, Gurven MD, Trumble BC, Kaplan H, Buetow K. Arizona State University; Phoenix Children's Hospital; University of Arizona; University of Southern California; Monash University; San Simon University; Tsimane Health and Life History Project; MemorialCare Health Systems; University of Utah; University of California, San Diego; University of California, Irvine; University of Missouri-Kansas City; Providence Health; University of New Mexico; Al-Azhar University; Renown Institute for Heart and Vascular Health; Chapman University; University of North Carolina at Chapel Hill; Université Toulouse 1 Capitole; University of California, Santa Barbara.

Background: The genetic etiology of Cognitive Impairment (CI) is poorly understood. This is due, in part, to the complexity of diverse genetic and environmental risk factors in large, heterogeneous study populations. To overcome this obstacle, we examined a population with low genetic heterogeneity and fewer risk factors commonly found in industrialized populations - the Tsimane of Bolivia (N=353; mean age=69 years [60–93 years]). The Tsimane are a geographically isolated forager-horticulturalist population with high levels of physical activity and low prevalence of coronary artery disease, hypertension, and diabetes, even at advanced ages. The absence of these typical Alzheimer's Disease (AD)-related comorbidities provides a novel opportunity to isolate aspects of CI that are often intertwined with cardiometabolic and other non-communicable chronic diseases.

Methods: CI was determined from field evaluations using a locally translated and adapted cognitive battery, mental status examination, informant interview, and neurological evaluation (CI=31, AD=1). Genome-wide variation was characterized using the Infinum Multi-Ethnic Global Array (1,754,170 SNPs) and evaluated with a novel analytic tool that uses biologic processes as the unit of analysis — Pathways of Distinction Analysis (PoDA). PoDA captures interactions across the multiple genes within a network and assesses significance via empiric resampling. A catalog of 1167 curated networks representing the diversity of biologic function was evaluated.

Results: The pathway that most significantly distinguishes individuals with CI from those without impairment is the KEGG Alzheimer's Disease Pathway (Distance Score [DS]=3.23; FDR-adjusted pDS<0.001). This pathway is composed of 169 genes that capture the major processes associated with AD. Refined analysis identified a subset of 35 genes that is associated with a 6-fold difference (OR=6.26; pOR=1.21x10⁻¹²) in relative risk for prevalent CI vs. no impairment. Those genes are involved in insulin signaling, calcium signaling, and mitochondrial oxidative phosphorylation subcomponents of the AD Pathway. It also includes variation within the AD risk loci APBB1 and MAPT (Figure 1).

Conclusions: In a population with minimal cardiometabolic disease, pathway-based genome analysis objectively identifies subcomponents within the AD pathway tied to cellular energy metabolism as important in CI. Following validation in larger, heterogenous populations, these components may provide targets for prevention and intervention.

NEUROIMAGING CORRELATES OF FUNCTIONAL MOTOR CHANGES IN COGNITIVELY IMPAIRED COHORTS. Bergamino M, Keeling E, Schaefer S, Burke A, Prigatano G, Stokes A. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: Mild cognitive impairment (MCI) is an intermediate state between normal aging and dementia. Subjective memory complaints (SMC) are also common in older people and it is often related to neuropsychiatric disorders such as anxiety and depression. Few studies have assessed the underlying neuropathological changes associated with SMC and MCI, which is critical for clinical management of these disorders. MRI-based biomarkers with diffusion tensor imaging (DTI) are sensitive to white matter (WM) microstructure and may be useful to study these changes. In this preliminary study, we analyzed WM microstructural differences between groups of healthy controls (HC), SMC, and cognitive impairment (AD+MCI; CI). WM microstructure differences was assessed by free-water (FW) corrected DTI (FW-DTI) metrics and by the peak width of skeletonized mean diffusivity (PSMD). Since new research shows that motor function may be impaired in preclinical AD, this study explored voxel-based correlations between a functional motor measure (two-bean transfer) and DTI metrics.

Methods: This study included 7 HC (mean age (standard deviation (S.D.)): 72.7 (8.0)), 8 SMC (mean age (S.D.): 67.8 (4.9)), and 9 CI (mean age (S.D.): 74.1 (5.8)). A standard neuropsychological examination was conducted for SMC and CI cohorts to confirm participants' cognitive status. Subjects also performed two motor tasks. The first was the modified version of the Halstead Finger Tapping Test, and the second involved using a spoon to transfer two raw kidney beans at a time from one cup to another with their nondominant hand. Performance on this task was quantified as the intrasubject standard deviation (nISD) in trial time across four practice trials. Diffusion MRI was performed at 3T (Philips) using a multi-shell acquisition with 60 diffusion directions ($b=500, 1000, \text{ and } 2500 \text{ s/mm}^2$) and one B0 image. DTI pre-processing was performed by MRtrix3, FSL, and ANTs. Free-water (FW) maps were computed by Dipy. To study differences across groups, the one-way ANCOVA test was performed in R with age and sex as covariates. PSMD was computed using FSL and an in-house script. Voxel-based correlations were studied using a linear model with R.

Results: Differences in nISD across groups were found (Kruskal-Wallis: $\chi^2=6.28$; $p=0.043$). ANCOVA identified differences across groups ($FWE<0.05$) for FW-FA and FW index, mainly in corpus callosum (CC), anterior corona radiata, and fornix. Post-hoc analyses showed higher FW-FA in HC than SMC and CI. Additionally, compared with CI group, SMC showed higher FW-FA. On the other hand, SMC and CI displayed higher FW index than HC, while CI showed higher FW index than SMC. Significant correlations with nISD were found mainly in the anterior/posterior limb of internal capsule. PSMD analysis in the whole brain showed significant differences across groups.

Conclusions: The FW correction algorithm for DTI is able to minimize the inaccuracies associated with partial volume effect, while PSMD is a robust marker for cerebral small vessel disease based on DTI and has been used previously to study AD. Here, both FW-DTI and PSMD analysis showed microstructural WM differences across HC, SMC, and CI cohorts. Large differences across groups were found primarily in the CC; additionally, both methods were able to distinguish CI from SMC. Moreover, FW-DTI found significant correlations with the nISD score. In conclusion, the use of FW-DTI and PSMD may provide novel insight into sub-voxel neurodegenerative processes and might warrant further exploration in more SMC and CI patients.

NOVEL IMAGING MARKERS FOR ALTERED CEREBROVASCULAR MORPHOLOGY IN AGING AND ALZHEIMER'S DISEASE. Deshpande A, Elliott J, Laksari K. University of Arizona; Arizona Alzheimer's Consortium.

Background: Altered brain vasculature is a key phenomenon in several neurologic disorders. Alzheimer's disease (AD), one of the most common neurodegenerative diseases, is hypothesized to possess significantly altered architecture of the brain vascular network. Despite our expanding knowledge of the significance of cerebrovascular alterations in AD at the cellular and microvascular level, which is due to plaque and amyloid deposition as well as pathological structural alterations in the endothelium, our understanding of morphological changes in the major vessels in AD is still in early phases and has mainly been limited to animal studies. Reduced cerebral blood flow (CBF) and perfusion, observed in neurodegenerative diseases, exacerbates neuronal degeneration and amyloid deposition, reduces elastin production, causes distensibility and autoregulation loss, and increases wall shear stress. These developments could lead to significant morphological changes throughout the brain vasculature, including increased vascular stiffness, decreased diameters, and possibly higher tortuosity and fractality in AD brain vessels. These changes can often precede clinical symptoms and may serve as early disease markers. Consequently, studying the quantitative and qualitative changes in the cerebral vascular network due to aging and disease is pertinent to understanding brain health and may impact diagnosis, and treatment of neurologic disorders.

Methods: This paper presents a quantitative assessment of vascular morphology in healthy and diseased adults including changes during aging and the anatomical variations in the Circle of Willis (CoW). We used our recently developed and validated automatic algorithm to segment and extract geometric features of the cerebral vasculature from MR angiography scans of 175 healthy subjects, which were used to create a probabilistic atlas of cerebrovasculature and to study normal aging and inter-subject variations in CoW anatomy. Subsequently, we quantified and analyzed vascular alterations in 50 Alzheimer's disease (AD) patients with varying levels of dementia, defined using the CDR scale and extracted the cerebral vascular networks and their corresponding geometric properties. The quantitative extracted geometric features were compared to the healthy average morphometric features. The data was then further divided into two – early-mild (CDR 0.5 and 1) and moderate-severe (CDR 2 and 3) dementia levels.

Results: We determined that the CoW is fully formed in only 35% of healthy adults and found significantly ($p < 0.05$) increased tortuosity and fractality, with increasing age and also with disease. The AD patients' vascular network is characterized by higher tortuosity and fractality, greater number of branches and a smaller average diameter. The association of these vascular structural alterations with disease were seen across the AD groups, when adjusted for age. As dementia levels increase from early-mild to moderate-severe, we observed significant differences in the vascular features between groups with varying levels of dementia, specifically higher tortuosity, fractality, number of branches, and a smaller average diameter. More pronounced twists and loops in the AD vasculature are not observed in healthy subjects and is corroborated with studies which reported similar behavior of cerebral vessels in mice.

Conclusions: Despite paucity of longitudinal datasets, the specific geometric features and quantitative comparisons demonstrate the potential for using vascular morphology as a non-invasive imaging biomarker for neurologic disorders.

OLDER ADULT WILLINGNESS TO ENROLL IN AD-FOCUS RECRUITMENT REGISTRIES AND TO PARTICIPATE IN REGISTRY-SPECIFIC ACTIVITIES: A NATIONALLY REPRESENTATIVE SAMPLE OF OLDER ADULTS IN THE UNITED STATES. Bleakley A, Maloney E, Hennessy M, Karlawish J, Harkins K, Nosheny R, Langbaum JB. University of Delaware; University of Pennsylvania; University of California San Francisco; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Participant recruitment registries are tools used to refer potentially eligible participants to studies. Currently, most U.S. Alzheimer's-focused registries underrepresent non-White participants and men. If registries are going to play a role in recruitment for Alzheimer's disease (AD)-focused studies, they need to be representative of the population in terms of racial, ethnic and gender diversity. The aim of this study was to assess the willingness of White, Black, and Hispanic older adults in the US to join an AD-focused registry and to perform a range of behaviors or tasks that enrollment in the registries can entail.

Methods: We conducted a national, online survey in June 2021 of 1,501 adults ages 50-80, with oversamples of Black and Hispanic for group comparisons (mean age 62.3 SD (7.6), 51% female, 21% Hispanic, 20% Black, 14% family history of AD). Respondents were asked questions to assess intention to join a registry and complete 7 behaviors or tasks that joining a registry may require (e.g., giving a DNA sample, giving a blood sample, completing surveys, and providing a family member's contact information). Overall, intention to join or complete the behaviors was assessed on a 7-point scale from -3 (extremely unlikely) to +3 (extremely likely).

Results: The mean overall intention to enroll in an AD-focused registry was -0.52 (SD 1.77); there were no differences by race and ethnic group or by gender. Of the 7 additional behaviors, the only statistically significant group difference was that women were more willing (M 0.081 SD 1.75) than men (M 0.055 SD 1.86) to take repeated cognitive testing. The 7 behaviors had high internal consistency (Alpha=.95) and were also difficultly ordered (Loevinger's H=0.76) so that most difficult behavior was providing a family member's contact information, followed by giving a DNA sample, and the easiest behavior was completing study questionnaires.

Conclusions: The results from this national survey did not identify differences in intention to join a registry by race, ethnicity, or gender, suggesting that differential enrollment rates are not driven by differences in willingness. The results will be used to develop culturally sensitive messaging to encourage enrollment into registries.

PERSONAL MENTAL TIME TRAVEL MAY BE AN IMPORTANT COGNITIVE MECHANISM BEHIND ALZHEIMER'S DISEASE RISK-RELATED REDUCTIONS IN EVENT CONSTRUCTION EPISODIC SPECIFICITY. Deffner AM, Stoica T, Thayer SC, Andrews-Hanna J, Grilli MD. University of Arizona; Arizona Alzheimer's Consortium.

Background: Previous research suggests that cognitively unimpaired older adult carriers of the apolipoprotein E e4 allele (APOE4) display a reduction in episodic specificity (i.e., vivid detail) when remembering and imagining personal events. While remembering and imagining involve "mental time travel" to the personal past or future respectively, it is not clear if personal mental time travel is an important mechanism behind this Alzheimer's disease risk-related reduction in episodic specificity. To help close this gap in knowledge, we investigated whether APOE4 carriers show reduced episodic specificity while engaged in atemporal, novel scene construction: a type of event construction that does not require mental time travel to the personal past or future.

Methods: Cognitively unimpaired older adult APOE4 carriers (N=35, Age M = 69.0) and neuropsychologically and demographically similar older adult non-carriers (N=39, Age M = 69.3), underwent an fMRI session and separately completed a battery of personal and non-personal event (re)construction tasks, including a scene construction task in which they narrated aloud what they were imagining when given atemporal, non-personal settings (e.g., standing on a train platform).

Results: Findings indicated that APOE4 carriers did not exhibit significantly reduced episodic specificity relative to APOE4 non-carriers regardless of total episodic details or ratio of episodic to nonspecific details (p 's > 0.53). Despite this lack of an Alzheimer's disease risk-related reduction in episodic specificity, these same APOE4 carriers exhibited reduced episodic specificity on a separate task requiring personal mental time travel into the past and future (p 's = .04). Furthermore, examining episodic specificity in these mental time travel and atemporal event (re)construction tasks in relationship with fMRI-derived resting state functional connectivity metrics suggested that personal mental time travel and atemporal event construction have distinct correlates within the default mode network. Specifically, whereas individual differences in episodic specificity during personal mental time travel was associated with connectivity within the medial temporal lobe subsystem, individual differences in episodic specificity during atemporal scene construction was associated with connectivity between the medial temporal lobe subsystem and medial prefrontal cortex.

Conclusions: Alzheimer's disease risk-related reductions in episodic specificity, as measured by APOE4 in clinically unimpaired older adults, may be more prominent when event (re)construction requires personal mental time travel.

PLASMA NEUROFILAMENT LIGHT CHAIN IN COGNITIVELY UNIMPAIRED LATE MIDDLE-AGED & OLDER ADULT APOE E4 HOMOZYGOTES, HETEROZYGOTES, & NON-CARRIERS FROM THE ARIZONA APOE COHORT. Ghisays V, Su Y, Malek-Ahmadi MH, Jansen WJ, Protas HD, Chen Y, Lee W, Luo J, Bauer RJ, Chen K, Caselli RJ, Zetterberg H, Blennow K, Reiman EM. Banner Alzheimer's Institute; Mayo Clinic, Scottsdale; Sahlgrenska University Hospital; University of Gothenburg; University College London; Hong Kong Center for Neurodegenerative Diseases; Arizona State University; University of Arizona; Arizona Alzheimer's Consortium.

Background: APOE4 gene dose, the number of apolipoprotein E - ϵ 4 (APOE4) ϵ 4 alleles in a person's genotype, is associated with higher Alzheimer's disease (AD) risk and younger median age at dementia onset. We previously found relationships between PET, plasma, and measurements of core AD CSF biomarkers in APOE4 gene dose. Here, we characterize longitudinal neurofilament light chain (NfL) changes in the Arizona APOE cohort, including cognitively unimpaired participants, with longitudinal plasma NfL measurements in APOE4 homozygotes (HMs), heterozygotes (HTs) and non-carriers (NCs).

Methods: Plasma NfL measurements were performed at the University of Gothenburg using a Single molecule array (Simoa) immunoassay. Annual log-transformed plasma NfL changes were compared with linear-trend and univariate ANOVA adjusted for age, sex, and education in 45 HMs, 107 HTs, and 201 NCs who were cognitively unimpaired, 47-85 years old and did not differ significantly in their age, sex, or educational level. Pearson r correlations with age and annual log-transformed NfL changes were assessed in 353 participants with at least 2 visits (range 2-6 visits with an average of ~3) and an average follow-up of ~7 years (range 1-12 years).

Results: Annual log-transformed NfL changes were linearly associated with APOE4 gene dose (linear trend HM>HT>NC, $P = 0.01$) and positively associated with age ($r = 0.31$, $P < 0.0001$). Pairwise comparisons from the univariate ANOVA adjusted for age, sex, and education ($P = 0.001$) showed significantly higher annual NfL changes in HM and HT groups versus NC controls ($P = 0.01$).

Conclusions: Age and APOE4 gene dose are associated with greater annual plasma NfL changes in CU subjects close to their estimated ages at clinical onset. Studies are needed to better elucidate relationships between different A β , tau, inflammatory, and other CSF, or blood-based biomarkers, and APOE4 gene dose at other ages and in larger subject groups.

POSTNATAL CHEMOPHENOTYPIC NEURONAL ALTERATIONS IN THE FRONTAL CORTEX, HIPPOCAMPUS AND CEREBELLUM IN DOWN SYNDROME. Perez SE, Moreno DG, Utagawa EG, Miguel JC, Arva NC, Schafernak KT, Mufson EJ. Barrow Neurological Institute; Ann & Robert H. Lurie Children's Hospital of Chicago; Phoenix Children's Hospital; Arizona Alzheimer's Consortium.

Background: Down syndrome (DS) people display a reduction in frontal cortex (FC), hippocampal and cerebellar volume attributed to prenatal proliferation/migration deficits, however, the effect of trisomy 21 upon the postnatal neuronal development remains under-investigated.

Methods: We examined the neuronal phenotypes within the FC, hippocampus and cerebellum obtained at autopsy from DS and neurotypically developing (NTD) subjects born at 28-weeks'-gestation up to 3 years of age using antibodies against non-phosphorylated neurofilament protein (SMI-32); calbindin D-28k (Calb), calretinin (Calr) and parvalbumin (Parv); neurogenesis doublecortin (DCX); proliferation Ki-67; amyloid precursor protein (APP)/beta-amyloid (A β); A β 1-42 and phosphorylated tau (p-tau, CP13 and PHF-1).

Results: Our findings showed a greater reduction in DS DCX-immunoreactive (-ir) cells in the FC and hippocampus. Both groups showed a similar distribution/number of SMI-32-ir cells in the hippocampus and cerebellum. FC SMI-32-ir cells appeared as early as 28'-weeks-gestation in NTD, but not until 196 weeks in DS. Although the distribution of Calb-ir neurons in the FC, hippocampus and cerebellum were similar between the youngest and oldest NTD and DS cases, the number of Calb-ir cells were significantly higher only in the NTD FC. Hippocampal Calr-ir cells and fibers were observed at all ages in DS, whereas Calr-ir fibers were mainly displayed in NTD cases. FC and cerebellar Calr-ir cell counts were comparable between groups. Parv-ir cells were found only in the cerebellum in DS and NTD. APP/A β -ir diffuse-like deposits were seen in the FC, hippocampus, and cerebellar cortex in DS and NTD. Only intraneuronal A β 1-42 immunoreactivity was detected in Purkinje cells in both groups. p-tau profiles were found in the FC and cerebellar cortex in the youngest DS and NTD cases.

Conclusions: These findings suggest that trisomy 21 affects the neuronal chemophenotype in postnatal FC, hippocampus and cerebellum that may contribute to cognitive impairment in DS.

PREDICTING BRAIN AMYLOIDOSIS WITH PLASMA B-AMYLOID42/40 AND MRI-BASED MORPHOMETRY FEATURES. Wu J, Su Y, Thompson PM, Reiman EM, Caselli RJ, Chen K, Wang Y. Arizona State University; Banner Alzheimer's Institute; University of Southern California; University of Arizona; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Biomarkers assisting early detection and intervention in Alzheimer's disease (AD) may be the key to therapeutic breakthroughs. One of the presymptomatic hallmarks of AD is the accumulation of beta-amyloid ($A\beta$) plaques in the human brain. However, current methods to detect brain $A\beta$ pathology are either invasive (lumbar puncture) or quite costly and not widely available (amyloid PET). The blood-based biomarker, like plasma $A\beta_{42}/A\beta_{40}$, enables more rapid and inexpensive screening of potential participants for brain amyloidosis. Additionally, our recent research has demonstrated that MRI-based hippocampal multivariate morphometry statistics (MMS) can be an effective neurodegenerative biomarker for predicting brain amyloid deposition. In this study, we demonstrate that the combination of these two state-of-the-art biomarkers could achieve superior performance in predicting the brain $A\beta$ burden assessed based on amyloid.

Methods: MMS are first extracted from MR images. As MMS have a larger dimension than the sample size, we used our previously introduced sparse coding algorithm, Patch Analysis-based Surface Correntropy-induced Sparse coding and max-pooling (PASCs-MP), to generate a low-dimensional representation of hippocampal morphometry for each subject. We randomly but consistently over subjects select patches of MMS on the hippocampal surface. Then, sparse-coding and max-pooling are used to generate representations for these subjects. Finally, we train binary random forest classifiers on the representations and the measures of plasma $A\beta_{42}/40$ from the people with different PET-based brain $A\beta$ positivity status and evaluate these classifiers with 10-fold cross-validation.

Results: From the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu), we identified 198 subjects with matching plasma $A\beta_{42}/40$ measures, florbetapir PET and T1-MRI scans, 98 subjects were amyloid positive and 100 were amyloid negative based on florbetapir PET and previously discussed processing pipeline and positivity threshold. We trained random forest classifiers on this dataset with different features, including plasma $A\beta_{42}/40$, MMS separately or jointly. For each experiment, we performed 10-fold cross-validation five times. The accuracy of predicting amyloid positivity with only plasma $A\beta_{42}/A\beta_{40}$ or only our MMS-based PASCs-MP representations is 0.72 and 0.80. But when we trained the model with both biomarkers, the accuracy increased to 0.87.

Conclusions: Although plasma $A\beta$ has been shown to be an adequate test to screen cognitively normal individuals for brain amyloidosis, combining it with our MRI-based hippocampal multivariate morphometry statistics may further improve the diagnosis accuracy of brain amyloidosis.

PRELIMINARY BASELINE BRAIN CORRELATES OF ACCELERATED VISUAL MEMORY DECLINE IN MIDDLE-AGE AND OLDER ADULTS WITH AUTISM: THE CASE FOR HIPPOCAMPAL FREE-WATER. Walsh MJM, Ofori E, Pagni BA, Chen K, Sullivan G, Braden BB. Arizona State University; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Research aimed at understanding cognitive and brain aging in adults with autism spectrum disorder (ASD) is growing, but critical longitudinal work in middle-age and older adults has yet to emerge. Adults with ASD struggle with tasks involving visual memory compared with neurotypical adults (NT). This may be related to differences in size or integrity of the hippocampus and its' primary structural connectivity pathway, the fornix. The aim of this study was to describe preliminary longitudinal aging trajectories in short- and long-term visual memory abilities in middle-age and older adults with ASD, compared with matched NT adults. In the presence of accelerated decline in the ASD group, we evaluated baseline multi-modal imaging metrics of the hippocampal system, including the relatively novel metric free-water, as potential predictors for longitudinal memory change in middle-age and older adults with ASD.

Methods: Middle-age and older adults with ASD (n=25) and matched NT adults (n=25) between the ages of 40 and 70 years were followed longitudinally at approximately two-year intervals (range 2-5 years). Participants completed the Wechsler Memory Scale III Visual Reproduction task. Longitudinal mixed models were run to detect group differences in memory change with baseline age and sex as covariates. Hippocampal volume was measured via T1-weighted MRI images with FreeSurfer. Fornix FA and hippocampal and fornix free-water were measured from diffusion tensor imaging (DTI) scans. Exploratory correlations were run between individual hippocampal system metrics and longitudinal slopes of visual memory change. Alpha was set at 0.05.

Results: There was a significant group by time interaction for long-term visual memory, such that middle-age and older adults with ASD declined faster than matched NT adults. There was no group by time interaction for short-term visual memory. Baseline hippocampal free-water was the only hippocampal system metric that correlated with long-term visual memory change in middle-age and older adults with ASD.

Conclusions: In one of the first longitudinal cognitive and brain aging studies in middle-age and older adults with ASD, findings suggest vulnerabilities for accelerated long-term visual memory decline, compared to matched NT adults. Further, baseline hippocampal free-water may be a predictor of memory change in middle-age and older adults with ASD. This relatively novel microstructure metric is thought to indicate atrophy in a way that is more sensitive to total structure volume. These preliminary findings lay the groundwork for future prognostic applications of MRI for cognitive aging in middle-age and older adults with ASD.

RECRUITED COHORT DIFFERENCES BETWEEN TWO VERSIONS OF A WEB-BASED STUDY OF COGNITION. Huentelman M, De Both M, Johnson M, Hoscheidt S, Irwin K, The Precision Aging Network Research Team, Ryan L. Translational Genomics Research Institute; Precision Aging Network; University of Arizona; Arizona Alzheimer's Consortium.

Background: The demographic composition of human research study cohorts is influenced by many factors. Our internet-based research study MindCrowd (located at mindcrowd.org) was launched in January of 2013 with the goal of facilitating study cohort diversity across the age spectrum, race-ethnic categories, gender identities, educational attainment levels, and geographical locations. During the last 16 months, we redesigned our study site and modernized several features, including the ability to participate via any type of smartphone device. In this abstract, we compare two MindCrowd cohorts to identify compositional differences across demographic, health, medical, and lifestyle variables.

Methods: The pre- (“mc1”) and post-launch (“mc2”) versions of MindCrowd cohorts were examined. The launch date for mc2 was June 16th, 2022, and this was utilized as the mc1 to mc2 cohort transition date. Of note, the recruitment period for mc1 is 116 months and for mc2 it was 2 months at the time of writing. Minor differences exist between the exact wording of the demographic, health, lifestyle, and medical questions on the two versions of the site and this was considered during analysis and only those comparisons that could be made exactly between mc1 and mc2 are reported in this abstract. MindCrowd includes testing through the use of simple visual reaction time (svRT) and paired associate learning (PAL) tasks. These tasks remained the same between mc1 and mc2, however, it should be noted that the svRT task utilizes more trials in the mc2 version.

Results: The recruitment rate for mc2 is approximately double that for mc1 with over 9,000 participants joining mc2 each month. The participant age distribution for mc2 is shifted toward older adult participants with over 70% of the cohort reporting their age as 50 years and older. Educational attainment in mc2 is, on average, lower than that of mc1 with significant increases in the number of participants reporting their max attainment as high school diploma and less (~20% in mc2). American Indian and Alaska Native recruitment has doubled in mc2 (to 1.4%) while Asian, Native Hawaiian, and Black/African American remain comparable to mc1. The Hispanic/Latino composition of mc2 is 18.2%; more than double that observed in mc1 (8.2%). Recruitment of individuals from rural zip codes is increased in mc2 (8.8% vs. 6.2% in mc1).

Conclusions: Although mc2 is still relatively new, the data suggest that mc2 has significant advantages over mc1 for recruitment of older adults, Hispanic/Latino individuals, participants with lower educational attainment, and individuals from rural zip codes. In general, mc2 has significantly higher daily recruitment rates when compared to mc1. These data suggest that the changes instituted during the development of mc2 – the most significant of which was the allowance of smartphone-based study participation – improve the recruitment of typically difficult to recruit and underserved groups.

Funding: MindCrowd receives support from the Mueller Family Charitable Trust, the Flinn Foundation, the State of Arizona DHS in support of the Arizona Alzheimer's Consortium, and the National Institutes of Health – National Institute on Aging (U19AG065169).

REPRODUCTIVE HEALTH DATA AND ITS RELATIONSHIP TO BASELINE BRAIN IMAGING AND COGNITIVE MEASUREMENTS IN COGNITIVELY UNIMPAIRED FEMALE PSEN1 E280A MUTATION CARRIERS AND NON-CARRIERS FROM THE API ADAD TRIAL. Ghisays V, Vila-Castelar C, Giraldo-Chica M, Acosta-Baena N, Protas HD, Malek-Ahmadi MH, Chen Y, Luo J, Lee W, Bocanegra Y, Muñoz C, Herrera K, Hu N, Sink KM, Clayton D, Alvarez S, Langbaum JB, Chen K, Su Y, Tariot PN, Quiroz YT, Lopera F, Reiman EM, Rios-Romenets S, API ADAD Colombia Trial Group. Banner Alzheimer's Institute; Universidad de Antioquia; Massachusetts General Hospital, Harvard Medical School; Genentech Inc.; Hospital Pablo Tobón Uribe; Arizona State University; University of Arizona; Arizona Alzheimer's Consortium.

Background: The impact of sex steroid hormones on Alzheimer's disease (AD) remains to be further clarified. Research suggests that shorter reproductive span, late menarcheal age, early menopause, oophorectomies and hysterectomies, are associated with increased dementia risk. We examined reproductive health and its associations with brain imaging and cognitive measurements in unimpaired female Presenilin 1 (PSEN1) E280A mutation carriers and non-carriers from the Alzheimer's Prevention Initiative Autosomal Dominant AD (API ADAD) Trial (NCT01998841).

Methods: A total of 151 cognitively unimpaired 30-53 year-old females (101 PSEN1 mutation carriers and 50 non-carriers) were included. Reproductive health data (i.e., menarcheal age, number of pregnancies, deliveries, miscarriages, and living children) from all participants were examined, as well as the extent to which menarcheal age was related to age-adjusted baseline 1) cortical amyloid plaque burden (florbetapir PET), 2) Precuneus cerebral glucose metabolism (fluorodeoxyglucose PET), 3) hippocampal volume (3TMRI), and 4) the API ADAD preclinical cognitive composite score, which includes the MMSE Orientation score, CERAD Word List Delayed Recall and Constructional Praxis, Multilingual Naming Test and Raven's Progressive Matrices subset. We examined associations with the cognitive and brain imaging measures corrected for multiple comparisons (Bonferroni).

Results: Carrier and non-carrier females did not differ on number of pregnancies, deliveries, miscarriages, or living children. Female carriers had a significantly younger menarcheal age than non-carriers (12.8 ±1.5 versus 13.7±1.6 years, $p = 0.007$, Bonferroni). Among carrier females, older menarcheal age was associated with lower scores on the Raven's test (Bonferroni: $r = -0.28$, $p = 0.035$). Menarcheal age was not associated with scores on the cognitive composite or other individual subtests, or with brain imaging measures.

Conclusions: Our findings suggest reproductive health data did not differ between carrier and non-carrier females, except for a slightly younger menarcheal age compared to non-carriers, and that menarcheal age may have a very limited impact on brain pathology and function at preclinical stages of ADAD. Longitudinal studies with larger samples are needed to clarify the extent to which earlier menarcheal age may be related to changes in cognitive function in mutation carrier females transitioning from preclinical to clinical stages.

SALUTARY BIO-PSYCHO-SOCIAL EFFECTS OF NATURE AWARENESS INTERVENTION ON OLDER ADULTS WITH LONG-COVID AND BRAIN FOG: A PILOT RANDOMIZED CONTROLLED TRIAL. Ng TKS, Tanner L, Thomas R, Wu S, Lim E, Maxfield M, Larkey L. Arizona State University; National University of Singapore; Arizona Alzheimer's Consortium.

Background: Approximately 20% of COVID-19 survivor reported ≥ 1 lingering symptom 8 weeks post-infection, characterizing a clinical syndrome called the long-COVID, or scientifically known as the Post-Acute Sequelae of SARS-CoV-2 infection [PASC]. Although primarily a respiratory disease, long-COVID has multiple impacts on other bodily systems, including "brain fog", i.e. cognitive impairment, and impair quality of life. Two biological contributors to long-COVID are elevated pro-inflammatory markers and dysregulated gut microbiota, which are also risk factor for Alzheimer's Disease (AD). Compounded with the existing increased risk in older adults, long-COVID-associated biological dysregulations will likely further increase the risk of AD in older adults with long-COVID and cognitive impairment (OACovCI). Addressing the scarcity of clinically effective intervention for long-COVID and informed by our previous trials on horticultural therapy and mindfulness intervention, this trans-disciplinary project will pilot an RCT on Nature Awareness Intervention (NAI) to examine if NAI is feasible and efficacious with OACovCI.

Methods: NAI incorporates active ingredients of mindfulness intervention and HT, encompassing exposure to nature, promoting mindfulness, and enhancing social connectedness. We will examine if NAI is feasible and efficacious with OACovCI. We will implement a single-(assessor-) blinded, wait-list-controlled, pilot RCT (N=60; 30 NAI, 30 wait-list) with community-dwelling OACovCI. Participants will be randomized to NAI (treatment) or wait-control and engage in weekly 1-hour in-person group interventions for the first 2 months and biweekly sessions for the subsequent 3 months.

Results: Recruitment and baseline assessments are on-going. We will determine the feasibility of the trial with OACovCI, compared to a waitlist control arm, using quantitative criteria, including recruitment, retention and attendance rates, and qualitative criterion, i.e., acceptability. We will also explore NAI's intervention effects, i.e., the "IFs", and mechanisms, i.e., the "HOWs". First, we will investigate pre- and post-intervention levels of outcome measures, i.e. self-report cognitive impairment, neuropsychological test battery and health-related quality of life measures, and mechanistic measures, i.e., blood, saliva and gut microbiome biomarkers. Second, we will examine the longitudinal and temporal associations between the outcome and mechanistic measures.

Conclusions: This project is timely and promotes a paradigm shift, initiating an inter-and multi-disciplinary team examining a novel non-pharmacological intervention, to improve care for OACovCI. This trial will provide preliminary data on the feasibility, efficacies, and exploratory mechanisms of a novel non-pharmacological intervention for OACovCI. The bio-specimens collected from this trial will enable exploratory biomarkers analyses with future funding. Long-term follow up with the same participants could also be performed in the future.

SEROTONIN REUPTAKE INHIBITORS ARE ASSOCIATED WITH LESS AMYLOID-B BURDEN SPATIAL EXTENT IN MILITARY VETERANS WITH ONLY PTSD, BUT NOT WITH TBI OR COMORBID PTSD/TBI: PRELIMINARY PET FINDINGS FROM ADNI-DOD PROJECT.

Chen K, Goradia DD, Chen Y, Luo J, Devadas V, Jagust W, Mackin S, Su Y, Landau S, Weiner M, Reiman EM. Banner Alzheimer's Institute; Arizona State University; University of Arizona; UC Berkeley; UC San Francisco; Veterans Affairs Medical Center; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Some but not all studies suggested association of serotonin reuptake inhibitors (SRIs) with a reduction in "magnitude" of amyloid- β (A β) plaque burden. Using PET images from ADNI-DOD and a voxel-based Majority Count Algorithm (MCA), we demonstrated that cognitively unimpaired veterans with post-traumatic stress disorder (PTSD) had significantly more cerebral voxels with lower rather than higher florbetapir standard uptake value ratios (voxel-based $P < 0.05$), reflecting A β burden reduction in "spatial extent" [Chen, AAIC 2018]). We postulated that this finding might relate their SRI use. Here, we investigate the impact of SRI use on the spatial extent of A β burden among ADNI-DOD veterans with PTSD, comorbid PTSD and traumatic brain injury (TBI), and TBI.

Methods: Statistical Brain Mapping (SPM12) adjusted for age, MMSE, education and APOE4 allele, a voxel-based $P < 0.05$ threshold, and MCA which is free of multi-comparisons (Stern, NEJM, 2019) were used to compare the greater versus lower number of cerebral voxels with higher A β burden in SRI non-users versus users in 6 groups. They are 1) PTSD alone (n=76), 2) PTSD or TBI (n=115), 3) comorbid PTSD/TBI or TBI (n=126), 4) PTSD, PTSD/TBI or TBI (n=202), 5) PTSD/TBI (n=87) and 6) TBI alone (n=39).

Results: SRI non-users had a significantly larger number of cerebral voxels than users with higher A β burden in the first four groups: 1) 28,539 in non-users versus 70 in users (voxel count ratio VCR=551) in PTSD; 2) 3,573 versus 21 (VCR=170) in PTSD or TBI; 3) 22,927 versus 1,162 (VCR=20) in comorbid PTSD/TBI or TBI; and 4) 7,569 versus 1,481 (VCR=5) in PTSD, comorbid PTSD/TBI or TBI, all MCA $p < 0.001$. In contrast, 5) SRI non-users and users did not differ in the number of cerebral voxels with higher A β burden in PTSD/TBI (3,209 versus 4,027, VCR=1, MCA $p = 0.48$); and 6) non-users had a significantly smaller number of cerebral voxels than users with higher A β burden in TBI (60 versus 11,715 VCR=0.005, MCA $p < 0.001$).

Conclusions: SRIs contribute to spatially less extensive A β burden in PTSD, more extensive A β burden in TBI, and intermediate/opposing effects in combinations of these conditions. Finding confirmation and mechanism clarification are needed.

SEX- AND APOE-SPECIFIC TRANSCRIPTOMIC SIGNATURES IN ALZHEIMER'S DISEASE: AN AZ-ADRC-RESEARCH EDUCATION SCHOLARS TEAM SCIENCE PROJECT. Vitali F, Raikes A, Hernandez GD, Yin F. University of Arizona; University of Arizona College of Medicine Tucson; Arizona Alzheimer's Consortium.

Background: Age, female sex and the APOE ϵ 4 allele are among the top risk factors for developing late-onset Alzheimer's disease (LOAD). Precision medicine for AD drug development necessitates the targeting of specific biological pathways that drive AD pathology. To date, while the individual effect of sex or APOE has been extensively studied, genes and biological pathways that are either commonly or uniquely altered by these two factors are less understood. Here, we capitalized on existing transcriptomic data to identify LOAD-associated transcriptomic signatures as a function of both sex and APOE genotype.

Methods: Brain RNA-Seq datasets from the ROSMAP (syn8456637) were obtained from the RNA-Seq Harmonization Study on AMP-AD. After excluding samples with incomplete demographic information, including APOE genotype, postmortem interval (PMI), and age of death (AOD), we retained a total of 369 frontal cortex samples from APOE ϵ 3/ ϵ 3 and APOE ϵ 3/ ϵ 4 individuals. Of these, 209 had an AD diagnosis (143 female and 66 males) and 160 were normal controls (92 females and 68 males). RNA-Seq gene counts were normalized using the trimmed mean of M values. For each sex-genotype condition, differentially expressed genes (DEGs, p-value < 0.05) between individuals with LOAD and cognitively normal controls were identified using a generalized linear regression model (GLM) with PMI, RNA integrity number (RIN), and AOD as covariates. Gene Set Enrichment Analysis (GSEA) was subsequently performed using Gene Ontology Biological Processes (GO-BP) accounting for the fold change of identified DEGs. Redundant GO-BP enriched terms were removed by computing semantic similarity of identified (adjusted p-values < 0.05) GO-BP terms based on an information content-based method (GOSemSim). A similarity cut-off of 0.6 was set to retain only non-redundant terms. Comparison analyses were then conducted to identify common and unique DEGs and enriched GO-BPs across sex-genotype conditions.

Results: Across all four sex-genotype conditions, APOE ϵ 3/ ϵ 3 female LOAD brains exhibited the greatest number of DEG transcripts (n = 11,851) while APOE ϵ 3/ ϵ 3 males exhibited the least (n = 714), when compared to their sex- and genotype-matched controls. Further, nine DEGs that are shared across all comparisons were identified (TMCC2, TAPT1-AS1, SLC6A12, PRELP, PITPNM1, MRGPRF, KIF5A, ARHGEF10, and APLN). Collectively, these genes are involved in metabolic processes, synaptic function, myelination, and GPCR signaling. GSEA analyses identified comparable numbers of LOAD-enriched pathways in female groups (both APOE ϵ 4 carriers and non-carriers) and male APOE ϵ 3/ ϵ 4s (n = 144-155 GO-BP terms), whereas APOE ϵ 3/ ϵ 3 males exhibited the fewest enriched terms (n = 13). Identified GO terms included pathways related to metabolism, cellular responses and regulation, and immune response regulation. There were no common GO-BP terms across all sex-genotype conditions.

Conclusions: Our analyses provide evidence of sex and APOE genotype specific transcriptomic signatures and biological processes altered in LOAD brains. Our findings suggest significantly greater transcriptomic dysregulation in female APOE ϵ 3/ ϵ 3 brains despite having a similar extent of affected biological pathways as the other as other sex-APOE conditions. In contrast, a significantly smaller number of affected biological processes were identified in male APOE ϵ 3/ ϵ 3s despite having comparable transcriptomic dysregulation as the male APOE4 carriers but less than the female groups. These analyses provide rationale to develop risk factor-specific therapeutics for the prevention and treatment of LOAD by considering the interaction between biological sex and APOE genotype.

SEX-DEPENDENT CHANGES IN LEARNING AND FLEXIBILITY DURING AGING IN MICE.

Lyle T, Truong V, Bowser S, Bimonte-Nelson H, Verpeut J. Arizona State University; Arizona Alzheimer's Consortium.

Background: Mapping how biological pathways change as the brain ages is critical to understanding why cognition wanes across the lifespan. Interestingly, specific dementias are sex-specific and while females are more likely to be diagnosed with Alzheimer's disease, males are at a greater risk for vascular dementia. There is a particular deficit in research studying the female brain and aging, which is striking as women diagnosed with dementia outnumber men 2 to 1 worldwide. 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. In females, a reduction of estrogen can reduce gray matter volume, and in rodent models, estrogen-containing hormone therapy has been shown to attenuate some forms of cognitive decline. Understanding sex-dependent trajectories in cognitive and brain changes with aging and Alzheimer's disease is critical to discovering novel mechanisms driving these effects, as well as new therapeutics. To determine how cognition changes across the lifespan, both male and female mice were studied to elucidate the trajectory of cognitive decline. We hypothesized that female mice will exhibit superior performance to males when juvenile, replicating our pilot data, but will undergo a more drastic cognitive decline than males into middle-age, thereby rendering related interaction with sex for cognitive flexibility.

Methods: Cognitive performance was assessed in C57BL/6J juvenile (postnatal day 21) and middle-aged (10 months old) mice ($n = 12$ per group) using a visual discrimination touchscreen apparatus. Mice were trained to discriminate between two shapes on a touchscreen and the correct shape was paired with a liquid reward of 20% sweetened condensed milk. The following measurements were quantified: learning rate, discrimination ability, initiation latency (time to start a trial), response latency (time to choose a shape), collection latency (time to collect reward), number of trials, and reversal ability. Animals were recorded during all components of the task to assess locomotion, velocity, and non-task related behaviors (grooming, rearing, climbing). After testing, mice were euthanized for neural structure (dendritic complexity and spine morphology) analysis in cognitive-associated brain regions, including the medial prefrontal cortex, infralimbic cortex, and anterior cingulate cortex.

Results: We found that juvenile female mice display faster initiation ($p < 0.01$) of each trial compared to males, indicating better performance in females. Further, while both male and female mice discriminated between two shapes equally well, juvenile female mice displayed increased reversal ability ($p < 0.01$), suggesting female-superior cognitive flexibility compared to males.

Conclusions: The current work will establish age-related changes in both males and females on this 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. Moreover, this neurobehavioral model could be used to evaluate transgenic Alzheimer's disease models to quantify changes in cognition, Alzheimer's disease-like pathology, and brain structure in comparison to the model's respective control population.

SEX-SPECIFIC GENE EXPRESSION OBSERVED IN HUMAN DEMENTIA WITH LEWY BODIES (DLB). Olney KC, Rabichow BE, Ross OA, Chang R, Fryer JD. Mayo Clinic, Scottsdale; Arizona State University; Mayo Clinic Graduate School of Biomedical Sciences; Mayo Clinic, Jacksonville; University of Arizona; Arizona Alzheimer's Consortium.

Background: The susceptibility of many neurological diseases varies based on an individual's genetic sex. For example, nearly two-thirds of Americans living with Alzheimer's disease are female, and it has been suggested that genetic females (46, XX) may develop more amyloid plaques due to mounting a more robust innate and adaptive immune response compared to genetic males (46, XY). On the other hand, genetic males (46, XY) are nearly 1.5X more likely to develop Parkinson's disease, characterized by the degeneration of neurons and the deposition of α -synuclein. Little has been reported on sex differences in dementia with Lewy bodies (DLB), which is characterized by α -synuclein protein accumulation in the form of Lewy bodies as well as the formation of amyloid in the brain.

Methods: Here we characterize sex differences in gene expression of 307 male and 146 female individuals diagnosed with DLB to determine if the molecular pathways contributing to this disease are shared between the sexes.

Results: At the time of abstract submission, our preliminary analysis compares gene expression differences between 58 DLB and 23 age-matched control brains of both sexes. Our results show that genes up-regulated in DLB brains compared to controls when including both sexes are enriched in pathways such as nervous system development, synaptic signaling, and glutamate receptor binding, while down-regulated pathways include oxygen transport and cytoplasmic translocation. When examining each sex separately, we identify that nearly all of the differentially expressed genes observed when utilizing samples from both sexes are driven mainly by the male XY samples, though at this stage, this could be due to sampling sizes rather than true differences arising due to biological sex.

Conclusions: We are analyzing this RNAseq dataset and including important covariates, such as APOE genotype, pathological burden, and comparison to other pathological groups. These studies will further identify the mechanistic pathways contributing to sex differences in neurological susceptibility and outcomes of dementia with Lewy bodies.

SHALLOW SHOTGUN METAGENOMIC SEQUENCING OF THE GUT MICROBIOTA THROUGHOUT IN 3XTG-AD MICE REVEALS THE LONGITUDINAL DYNAMICS OF GUT MICROBIAL SPECIES AND STRAINS. Borsom EM, Conn KA, Testo G, Hirsch AH, Orsini GM, Jaramillo SA, Lee, Caporaso JG, Cope EK. Northern Arizona University; Translational Genomics North; Arizona Alzheimer's Consortium.

Background: The microbial communities in the gastrointestinal tract, termed the gut microbiota, communicate bidirectionally with the brain via chemical signals. This communication, known as the gut microbiota-brain axis, may contribute to the development and progression of neurological diseases, including Alzheimer's disease (AD). However, most gut microbiota studies in patients living with AD and mice modeling AD to date focus on the bacterial communities using 16S rRNA gene sequencing, a technique with limited microbial resolution. In this study, we applied shallow shotgun metagenomic sequencing to fecal samples from 3xTg-AD mice at three timepoints during disease progression [2 months (pre pathology), 6 months (amyloidosis modeled), and 12 months (amyloidosis and tauopathy modeled)]. These data will be used to assess community composition and shifts in bacteria, archaea, fungi, and viruses at the species and strain level associated with three stages of AD progression.

Methods: To characterize the gut microbiota of 3xTg-AD and B6129F2/J (WT) mice, fecal samples were collected at 2, 6, and 12 months of age (n=6-8 mouse genotype/timepoint). DNA was extracted, the library was prepped with the Nextera XT DNA Library Prep kit, pooled, and sequenced on the Illumina NextSeq. Quality control was performed with fastqc, multiqc, and kneaddata. Kraken2 and Bracken were used to classify taxonomy and abundance. Alpha- and beta- diversity metrics, feature volatility, and differential abundance will be analyzed with QIIME 2.

Results: We generated a minimum of 500,000 sequences per sample. In 3xTg-AD mice, *Bacteroides fragilis*, *Turcibacter sanguinis*, *Turcibacter* sp. H121, and *Akkermansia muciniphila* were enriched. In WT mice, *Ligilactobacillus murinus* and *Bacteroides thetaiotomicron* were enriched. In our previous 16S rRNA gene sequencing on the same samples, we found increased abundance of *Turcibacter* sp., *Bacteroides acidifaciens*, and *Akkermansia muciniphila* in 3xTg-AD mice, and increased abundance of *Bacteroides* sp. and *Lactobacillus salivarius* in WT mice, demonstrating that the shallow shotgun analysis improves microbial resolution down to species level assignments. Analysis of alpha and beta diversity will show diversity within and across mouse genotype and age. Analysis of composition of microbiomes (ANCOM) will demonstrate differential abundances in microbial features between mouse genotype at 2, 6, and 12 months of age. Feature volatility will identify shifts in relative abundance of microbial species and strains across the three timepoints by mouse genotype.

Conclusions: To our knowledge, these findings are the first shotgun sequencing results to classify at the species level in 3xTg-AD mice. *Bacteroides fragilis* and *Akkermansia muciniphila*, enriched in 3xTg-AD mice, are associated with local and systemic inflammation, while microbes associated with beneficial host effects, including *Ligilactobacillus murinus* and *Bacteroides thetaiotomicron*, are enriched in WT mice. Further analysis of the gut microbiota at species and strain level will reveal the dynamics of these microbial communities in 3xTg-AD mice at 2, 6, and 12 months.

SIMULTANEOUSLY DEVELOPING INTERVENTIONS FOR LOW-, MIDDLE-, AND HIGH-INCOME SETTINGS: CONSIDERATIONS AND OPPORTUNITIES. Baker ZG, Nkimbeng M, Cuevas PEG, Quiñones AR, Kang HK, Gaugler JE, Hinton L, Gitlin LN, Shippee TP. Arizona State University; University of Minnesota; Centro Escolar University; Oregon Health and Science University; Chitkara University; University of California – Davis; Drexel University; Arizona Alzheimer’s Consortium.

Background: Most older adults reside in low- and middle-income countries (LMICs; by 2050 80%) but most research dollars spent on interventions to improve the lives of older adults are awarded to researchers in High-Income Countries (HICs; 99.9% of AD/ADRD studies). One approach to improve implementation of evidence-based innovations for older adults in LMICs is designing interventions that are relevant to LMICs and HICs simultaneously.

Methods: We propose that researchers in HICs could partner with stakeholders in an LMIC throughout the intervention design process to better position their intervention for implementation in that LMIC. We provide an example study from an adaptation of the Resources for Enhancing Caregiver Health (REACH) II in Vietnam, which did not use this strategy but may have benefited from this strategy. We then turn to several considerations that are important for researchers to contemplate when incorporating this strategy. Finally, we explore incentives for creating interventions that are relevant to both HICs and LMICs for funders, intervention designers, and intervention receivers.

Results: Considerations include considering cultural context, employing a conceptual framework to guide design, and involving relevant stakeholders. Opportunities include increased equity, benefits to older adults aging transnationally, potential for accelerating the research pipeline, monetary/prestige incentives, bidirectional knowledge transfer, and benefits for funders by maximizing the impact of their dollars. Finally, we make specific recommendations about how to employ a stakeholder partnership engagement process for the greatest possibility of success.

Conclusions: Although this is not the only strategy to bring interventions to LMICs, it may represent another tool in researchers’ toolboxes to help expedite implementation of efficacious interventions in LMICs.

SINGLE NUCLEI TRANSCRIPTOMIC PROFILES OF C9ORF72 PATIENTS WITH COGNITIVE SYMPTOMS SPANNING THE ALS-FTD SPECTRUM. Gittings LM, Alsop EB, Antone J, Singer M, Sattler R, van Keuren-Jensen K. Barrow Neurological Institute; Translational Genomics Research Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: It is well established that the C9orf72 repeat expansion mutation can manifest clinically as ALS, FTD or a combination of the two (ALS-FTD), however few studies have addressed the mechanisms underlying the cognitive aspects of the disease spectrum. Here, we use single nuclei RNA sequencing of frontal (disease affected) & occipital (non-disease affected) cortices from C9orf72 patients with cognitive symptoms spanning the ALS-FTD spectrum plus neurologically normal controls to uncover cell-type specific changes at the RNA level which may contribute to cortical degeneration.

Methods: Following quality control filtering, a total of 462,075 nuclei were sequenced from 25 C9orf72 patients (C9-ALS N = 10, C9-ALS-FTD N = 6, C9-FTD N = 9) and 9 controls.

Results: Visualization of the single-nuclei transcriptomes in uniform manifold approximation and projection (UMAP) space revealed separation of nuclei into 17 distinct clusters in both the frontal and occipital cortices, which could be annotated on the basis of the expression of known cell-type-specific markers. Differential gene expression (DEG) analysis was performed between each C9 phenotypic group and controls in selected cell types for both the frontal and occipital cortices. A comparison of the DEGs in the frontal and occipital cortices revealed that in ALS and ALS-FTD genes were similarly dysregulated in both brain regions. However, the relationship between the differentially expressed genes in these cortical regions in FTD was weaker suggesting that these brain regions have unique differences in the context of disease.

Conclusions: Analysis of this data is ongoing with the aim of identifying genes and cellular pathways that may underlie cortical degeneration in C9-FTD. Future studies will investigate the cellular mechanisms identified by the snRNA sequencing in iPSC- cortical neurons derived from C9 patients with clinical symptoms that span the ALS-FTD spectrum.

THE DATA MANAGEMENT AND STATISTICAL CORE (DMSC) AND THE NATIONAL ALZHEIMER'S COORDINATING CENTER'S (NACC) "DATA FRONT DOOR" (DFD) COLLABORATION. Amador R, Bauer III RJ, Parizek D, Saner D. Banner Alzheimer's Institute; University of Arizona; Arizona Alzheimer's Consortium.

Background: The Arizona Alzheimer Consortium (AAC) is part of the National Institute on Aging's (NIA) Alzheimer's Disease Research Centers (ADRCs) that contributes data using a prospective, standardized, and longitudinal clinical evaluations of the subjects. The 16 Uniform Data Set (UDS) evaluations forms are submitted to the National Alzheimer's Coordinating Center (NACC). These evaluations are carried out annually in-person or by telephone calls for as long as the participants is willing and able to collaborate. The established partnership with the Alzheimer's Disease Genetics Consortium (ADGC), the National Centralized Repository for Alzheimer's Disease and Related Disorders (NCRAD), and the NIA Genetics of Alzheimer's Disease Data Storage Site (NIAGADS), NACC provides a valuable resource for both exploratory and explanatory Alzheimer's disease research. The goal of this collaboration is to create one electronic platform that will integrate and connect all ADRC data streams to the NACC IDs. The biomarker and genetic metadata of all participants will be easily searchable through the electronic platform or "Data Front Door". This NACC data will be freely available to all researchers.

Methods: Using data collected from NIA-funded Alzheimer's Disease Research Centers (ADRCs) across the United States, NACC has developed and maintains a large relational database of standardized clinical and neuropathological research data. In partnership with the Alzheimer's Disease Genetics Consortium (ADGC), the National Centralized Repository for Alzheimer's Disease and Related Disorders (NCRAD), and the NIA Genetics of Alzheimer's Disease Data Storage Site (NIAGADS), NACC provides a valuable resource for both exploratory and explanatory Alzheimer's disease research.

Results: One-stop-shop for all data from the Alzheimer's Disease Research Centers (ADRC) Program. Longitudinal data: The UDS data are collected using a standardized evaluation of participants enrolled in ADRC clinics. Data are recorded directly on UDS forms (hard copy or electronic) during the evaluation process. Neuropathology data: The Neuropathology Data Set (NP) contains autopsy data for a subset of both MDS and UDS participants and Minimum Data Set (MDS) subjects. Imaging data: Magnetic resonance imaging, along with volumetric summary measures, are available for a subset of participants in the Uniform Data Set. CSF data: For some UDS subjects, CSF values are available for Abeta, P-tau, and T-tau. Genotypic and genomic data: Genotypic data (i.e., APOE status) is available at NACC for 75 percent of UDS participants, as well as information on whether the participant or their family has any known AD or FTLN mutations.

Conclusions: The synchronization of all these data streams and being able to connect them to NACC IDs will enable researchers to investigate and answer new questions in Alzheimer's disease.

THE LONG-TERM EFFECTS OF INTERMITTENT FASTING ON SIGNS OF AGING IN SENESCENCE ACCELERATED MOUSE-PRONE 8 (SAMP8) MICE. Meyers A, Kargari S, Crisan N, Mody A, Shim M. Arizona College of Osteopathic Medicine; Midwestern University.

Background: Aging is the greatest risk factor for Alzheimer's disease (AD). Intermittent fasting, a more palatable alternative to caloric restriction, has been shown to improve health conditions and to have many beneficial effects. However, the impact of intermittent fasting on cellular senescence has been rarely studied.

Methods: Senescence Accelerated Mouse-Prone 8 (SAMP8) mice have a shorter lifespan (9-12 months) and exhibit early-aging phenotypes including age-related deficits in learning and memory. We compared selected markers for senescence and aging in SAMP8 mice maintained on intermittent fasting (alternate day fasting) or ad libitum access to food for 9 months.

Results: Intermittent fasting suppressed the levels of senescence markers in visceral adipose tissue. In addition, aged SAMP8 mice subjected to intermittent fasting exhibited lower body weights, improved glucose tolerance, and reduced hepatic steatosis compared with the mice fed ad libitum. Moreover, intermittent fasting significantly improved the memory function of aged SAMP8 mice.

Conclusions: Our study suggests that the suppression of senescence may contribute to the beneficial effects of intermittent fasting and that slowing the rate of aging may improve the development and progression of AD. Analysis of aging phenotypes in other tissues is currently in progress.

THE TELOMERE PROTECTION PROTEIN RAP1 AND THE EPSILON ISOFORM OF GLIAL FIBRILLARY ACIDIC PROTEIN ACTIVATE GAMMA-SECRETASE ACTIVITY. Lewis KN, Carpenter R, Bae NS, Swanson MJ. Midwestern University; Arizona Alzheimer's Consortium.

Background: The accumulation of amyloid plaques is a hallmark of Alzheimer's disease (AD). The plaques consist of amyloid β ($A\beta$) peptides produced in the brain. Most are 40 amino acids long ($A\beta_{40}$) and are soluble. Occasionally, less soluble $A\beta_{42}$ peptides are made. Early-onset AD occurs due to mutations in the genes APP, PSEN1 or PSEN2. APP encodes amyloid precursor protein that is cleaved by β -secretase to make a 99 amino acid fragment (C99). C99 is cleaved by γ -secretase to produce $A\beta$ peptides. The PSEN genes encode the catalytic subunit of γ -secretase. Mutations in the APP and PSEN genes that cause AD do so by increasing total $A\beta$ production or by altering the ratio such that $A\beta_{42}$ makes up a higher percentage. Presenilin 1 (PS1), encoded by PSEN1, interacts with an isoform of glial fibrillary acidic protein (GFAP ϵ). Our lab identified GFAP ϵ in a yeast 2-hybrid screen as a protein that interacts with the telomere protection protein RAP1 (TERF2IP). The RAP1 protein has been shown to have non-telomeric functions in the cytoplasm. Our lab has shown under conditions of oxidative stress, nuclear RAP1 levels decrease while cytoplasmic RAP1 pools remain stable. Both shortened telomeres and oxidative stress have been linked to AD, and our data suggest that RAP1 may play some role. We investigated a possible role for RAP1 in AD using a yeast γ -secretase system.

Methods: We used E. coli expressed RAP1, GFAP ϵ and PS1 to test direct interactions among these proteins. The yeast *Saccharomyces cerevisiae* does not have APP or γ -secretase, allowing us to study these without other influences typically found in human cells. We introduced C99 fused to the yeast Gal4p transcriptional activator protein. When expressed, C99 is embedded in the plasma membrane, preventing Gal4p from entering the nucleus, and Gal4p-responsive genes are inactive. If C99 is cleaved by γ -secretase, Gal4p will enter the nucleus and activate its target genes. Thus, Gal4p-responsive gene expression is a measure of γ -secretase activity determined by growth assays (qualitative) and α -galactosidase assays (quantitative). γ -secretase was reconstituted in yeast by expressing all 4 subunits of the complex from plasmids. RAP1 and GFAP ϵ were also expressed to study their effects on γ -secretase activity. Enzyme-linked immunosorbent assays (ELISAs) were used to measure $A\beta$ production.

Results: Using E. coli expressed proteins, we determined that RAP1 and GFAP ϵ directly interact. When the genes encoding the γ -secretase subunits are expressed in yeast expressing C99-GAL4, we see strong activation of Gal4p-responsive genes, indicating robust γ -secretase activity. When RAP1 and GFAP ϵ are co-expressed, the activity of γ -secretase increased significantly. We have not been able to detect $A\beta_{42}$, but the $A\beta_{40}$ ELISA showed no differences in any sample, suggesting that RAP1 and GFAP ϵ may increase the amount of $A\beta_{42}$.

Conclusions: We established a reconstituted γ -secretase system in yeast to determine effects of specific proteins on $A\beta$ peptide production. The RAP1 telomere protection protein and GFAP ϵ modified the activity of γ -secretase, possibly by increasing $A\beta_{42}$ without affecting $A\beta_{40}$, which has implications for the development of Alzheimer's disease.

TRAILBLAZER-ALZ 3 TRIAL DESIGN AND RATIONALE. Tariot PN, Reiman EM, Alexander RC, Langbaum JB, Holdridge K, Ferguson MB, Yaari R, Sims JR, Zappone CA. Banner Alzheimer's Institute; Arizona State University; University of Arizona; Eli Lilly and Company; Arizona Alzheimer's Consortium.

Background: Genetic, biomarker and recent clinical trial evidence support the potential role of the amyloid pathway in the pathogenesis of Alzheimer's disease (AD). The pathophysiological process of AD begins more than two decades before symptoms first appear. This stage, in which individuals have preserved cognitive and functional abilities but AD pathophysiology is present, is known as preclinical AD. Consensus in the field is that compounds targeting the underlying disease process may have greater benefit when started earlier in the disease continuum, but no treatments that target AD pathology at the preclinical AD stage are currently available. Donanemab is an antibody specific for the N-terminal pyroglutamate A β epitope that is only present in mature brain amyloid plaques. The efficacy of donanemab in plaque removal and slowing cognitive decline in early symptomatic AD was demonstrated in the TRAILBLAZER-ALZ study. Exploratory analyses by baseline tau burden also suggest that clinical efficacy following donanemab treatment may be greater when initiated at earlier stages in the neuropathological cascade. TRAILBLAZER-ALZ 3 (NCT05026866), is a multicenter, randomized, double-blind, placebo-controlled Phase 3 trial that will evaluate the efficacy of donanemab, an antibody that binds to and removes deposited amyloid plaque, in preclinical AD.

Methods: Approximately 3300 men and women aged 55-80 years who meet entry criteria will be randomized in a 1:1 ratio to either donanemab (700 mg intravenously (IV) once every 4 weeks (Q4W) for the first 3 doses, then 1400 mg IV Q4W for the next 6 doses) or placebo (IV Q4W for 9 doses). Participants will be followed until approximately 434 participants experience a primary outcome event of clinical progression (an increase at 2 consecutive visits in the Clinical Dementia Rating Global Score (CDR-GS) from CDR-GS = 0 at baseline), so the total duration of study participation will vary for each participant. This trial will use a decentralized approach with visits conducted remotely in whole or in part, with a goal of increasing the number of eligible participants, including those from under-represented groups. All clinical and cognitive assessments will be conducted remotely by central raters.

Results: Secondary endpoints included to assess clinical progression will be discussed. To evaluate safety and tolerability of donanemab, this study will monitor spontaneously reported adverse events (AEs), MRI (for ARIA and emergent radiological findings), infusion-related reactions, and Columbia Suicide Severity Rating Scale. Serum, plasma, and whole-blood RNA samples for biomarker research will be collected at screening and throughout the study. Biomarker analysis will be performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics, mechanism of action, and variability of participant response (including safety). Plasma P-tau217 and other blood-based biomarkers will be used to further inform clinical outcomes and response to therapy. To assess the effect of donanemab on cerebral amyloid plaque burden and cerebral neurofibrillary tangle burden relative to placebo in the preclinical AD population, a subset of participants will undergo florbetapir and/or flortaucipir PET imaging.

Conclusions: TRAILBLAZER-ALZ 3 represents an innovative decentralized trial design with central raters. It includes a time-to-clinical-event model, a blood-based AD biomarker selection criterion, and potentially supportive AD biomarker endpoints. The results of this trial will help address the question of whether donanemab treatment with rapid lowering of cerebral amyloid plaque can delay or even prevent progression to the clinical stages of AD.

TRANSLATIONAL POTENTIAL OF JAX HUMANIZED APOE MICE: HIPPOCAMPAL VOLUME DECLINE IN AGED MOUSE EQUIVALENT OF 60-70 YR HUMAN. Raikes AC, Bhattra A, McLean JW, Wiegand JPL, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.

Background: Whole brain and hippocampal atrophy are the most prominent structural features of late-onset Alzheimer's disease (LOAD) and are accepted endpoints in many clinical trials. The APOE $\epsilon 4$ allele is the strongest genetic risk factor for LOAD, with the $\epsilon 4/\epsilon 4$ genotype associated with the greatest atrophy rates. To date, there is limited hippocampal volume reporting in preclinical APOE models. To assess the translational potential of a humanized APOE (hAPOE) mouse model, we report age, sex, and genotype effects on total brain and hippocampal volume.

Methods: High resolution ex-vivo MRIs were obtained from two separate cohorts of male and female hAPOE mice (Cohort 1: $n=52$, 18.47 ± 0.99 months; Cohort 2: $n=44$, 24.04 ± 0.64 months). A validated mouse brain atlas was used for volumetric analysis. Cohorts were analyzed separately with genotype by sex analyses of variance for total brain volume (sum of all regions in atlas) as well as left and right hippocampal volume as percent of total brain volume.

Results: In Cohort 1, hAPOE $\epsilon 4/\epsilon 4$ mice had significantly larger brains than hAPOE $\epsilon 3/\epsilon 3$ s or hAPOE $\epsilon 3/\epsilon 4$ s, with female hAPOE $\epsilon 4/\epsilon 4$ s having the largest brains ($p<0.001$). Regardless of genotype, females had smaller left ($p=0.006$) and right ($p<0.001$) hippocampi relative to males. In Cohort 2, females had greater total brain volume ($p=0.029$) without genotype effects. After correcting for brain volume, females additionally had smaller left ($p<0.001$) and right ($p<0.001$) hippocampal volumes. A non-significant main effect of genotype was observed in the left hippocampus ($p=0.076$), with female hAPOE $\epsilon 4/\epsilon 4$ mice having the smallest overall volumes.

Conclusions: Our findings capitalize on a large dataset ($n=88$) of high-resolution MRIs. At 18-20 months old (~60 human years), hAPOE $\epsilon 4/\epsilon 4$ mice had greater total brain volume than comparably aged hAPOE $\epsilon 3/\epsilon 3$ or hAPOE $\epsilon 3/\epsilon 4$ mice without hippocampal atrophy. However, hippocampal atrophy was evident when mice were aged to 24-25 months (~70 human years). These findings of larger brain volume and greater hippocampal atrophy in hAPOE $\epsilon 4/\epsilon 4$ carriers are consistent with large-scale AD imaging datasets. The timing of evident hippocampal atrophy in these mice also coincides with the global average age of clinical diagnosis. Based on these findings, the window for testing therapeutics will be limited to very old mice while the window for interventions preventing hippocampal atrophy will be greater.

TRANSLATIONAL POTENTIAL OF JAX HUMANIZED APOE MICE: TRAJECTORIES OF RESILIENT VERSUS SUSCEPTIBLE AGING BY SEX AND WEIGHT. Vitali F, Wiegand JP, Tucker A, Brinton RD. University of Arizona; Brunel University London; Arizona Alzheimer's Consortium.

Background: The translational potential of JAX humanized APOE (hAPOE) mouse models for Alzheimer's disease (AD) remains unsolved. Aging, chromosomal sex, and genetic risk factors interact to determine the trajectory of an individual's age-related biological changes and in turn may predispose individual risk or resilience to AD. In literature, there is growing evidence of inexplicable and accelerated weight loss prior to AD diagnosis. In support with growing evidence, we hypothesize that weight trajectories in our JAX humanized APOE mice cohort can be an early indicator of AD disease trajectory.

Methods: We used an autoregressive hidden Markov model (AHMM) to identify trajectories of JAX humanized APOE mice based on their longitudinal weight data. We assumed 10 hidden states to estimate proper trajectories. We ran 10 AHMM models to ensure stability and each model was run with 1500 iterations to reach convergence. The AHMM with maximum trace value was selected as the main model. The key trajectories were then identified by clustering together mice ending in the same hidden state. Weight data were collected from November 2018 to January 2022 for 1196 hAPOE mice (652M, 544F) for at least 3 time points ranging from 5 to 28 months of age. Genotypes included APOE3/3, APOE3/4 and APOE4/4.

Results: AHMM results identified 5 main weight trajectories for mice ending in one of the 5 most probable ending states. Of these, three states captured weight loss trajectories for 426 (36%) mice, one state was characterized by an increase in weight for 152 (36%) mice and 403 (13%) mice ending in a state stable with no significant weight loss or increase. The weight loss is more apparent in female, while weight increase is more typical of male mice.

Conclusions: This mouse cohort displays weight loss that may correspond to individuals exhibiting a hallmark inexplicable weight loss starting around 15/20 months (corresponding to human 50/55 years old) that can be symptomatic of the prodromal phase of AD.

TRAUMATIC BRAIN INJURY GENERATES ALZHEIMER'S DISEASE RELATED PROTEIN VARIANTS IN MOUSE MODEL BRAIN TISSUE. Panayi N, Schulz P, He P, Rowe RK, Sierks MR. Arizona State University; University of Colorado Boulder; Arizona Alzheimer's Consortium.

Background: Short-term detrimental effects of traumatic brain injury (TBI) include cognitive and behavioral deficits, while long term effects include an increased risk of developing neurodegenerative disease. Short term pathological changes after TBI result in parenchymal and axonal deposition of key protein variants associated with neurodegenerative diseases. We hypothesized that experimental TBI would result in the short term generation and longer term accumulation of key toxic protein variants associated with Alzheimer's Disease (AD) and related dementias (ADRDs), and that a subset of injured mice would develop behavioral deficits that correlate with specific protein variants implicated in ADRDs.

Methods: Adult male mice were subjected to a moderate TBI using midline fluid percussion injury (mFPI) or a control sham surgery. Sensorimotor function was tested using the rotarod and modified neurological severity score at 2, 5 and 7 days post-injury (DPI). Affective behavior (elevated plus maze and forced swim task) and cognitive function (novel object recognition task) were assessed at 7, 14 and 28 DPI. Brain tissue was collected at 7, 14, and 28 DPI and probed by immunohistochemical methods using a panel of antibodies to identify the presence and location of seven different toxic variants of amyloid-beta, tau, TDP-43, and alpha-synuclein that are associated with ADRDs. Levels of the different protein variants in different regions of the brain were assessed using Image J software. We correlated levels of the different protein variants in different brain regions with behavioral and cognitive performance.

Results: In general, levels of the ADRD related protein variants dissipated within 14 DPI and outcomes from behavioral tests also returned to baseline. However, individual mice displayed long-term effects in behavioral outcomes, and individual mice showed a persistent level of selected toxic protein variants in different brain regions that persisted to 28 DPI. We correlated the levels of protein variants in the different brain regions with the different behavioral outcomes. The 25 strongest correlations between protein levels and behavioral deficits were all between a specific oligomeric amyloid-beta variant (C6T) or a specific oligomeric tau variant (F9T). Both of these protein variants associate very strongly with and are excellent biomarkers for AD.

Conclusions: While the levels of most ADRD proteins were elevated shortly after TBI, in general levels declined and behavior deficits resolved within 14 days after injury. Here, we show that selected mice have chronic elevated levels of toxic protein variants associated with ADRDs, and that levels of specific AD related variants of amyloid-beta and tau correlate with chronic behavioral deficits. These results provide a mechanistic link for the long term increased risk of AD in human patients following TBI.

ABNORMAL GLIAL TDP43 INCLUSIONS IN A DEMENTIA CASE. Tremblay C, Intorcchia AJ, Mesch K, Walker JE, Arce RA, Qiji SH, Borja CI, Cline MP, Hemmingsen SJ, Aslam S, Mariner M, Suszczewicz KE, Krupp A, Martinez K, McHattie R, Stewart A, Beh ST, Beach TG, Serrano GE. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Abnormally phosphorylated TAR DNA-binding protein (TDP-43) in neurons was identified as the main pathologic feature of frontotemporal lobar degeneration (FTLD) and has been associated with an increased number of neurodegenerative diseases as well as being reported in normal aging. This case report describes an 80-year-old man that died with a clinical diagnosis of dementia due to probable Alzheimer's disease (AD). He was enrolled in the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) at Banner Sun Health Research Institute and his autopsy was done at the Brain and Body Donation Program (BBDP). He was clinically characterized with annual standardized movement and cognitive exams. He had begun showing symptoms at the age of 65 and had a 10-year history of memory dysfunction, slowly progressing to functional and behavioral changes. He showed marked executive dysfunction, accompanied with agitation, aggressive behavior, and impulsivity. He scored 8/30 on his last MMSE examination 1 year before death. He had no parkinsonism but had a non-specific tremor and features suggestive of progressive supranuclear palsy (PSP).

Methods: Neuropathological examination confirmed diagnoses of AD, FTLD with TDP-43 and progressive supranuclear palsy (PSP). Pathological observations include, presence of senile plaques and neurofibrillary tangles, and frequent phosphorylated TDP43 cytoplasmic inclusions in amygdala and hippocampus and up to moderate inclusions in temporal and frontal cortex. PSP pathological changes comprise the presence of typical glial lesions such as coiled bodies in oligodendrocytes and tufted astrocytes as well as neurofibrillary tangles in different nuclei. Other neuropathologic features allowed the diagnosis of hippocampal sclerosis, observable as a near complete loss of CA1 hippocampal neurons. Microscopic changes of Lewy body disease, restricted to the olfactory bulb, and non-specific glial tauopathy were also observed. This case was unusual because of its widespread highly dense TDP-43-positive histopathology, as well as the unusual morphology of TDP-43-immunoreactive cells that were resembling glia more than neurons. In order to confirm which cells were affected by TDP-43 double labeled fluorescent immunohistochemistry for TDP43 and microglia, astrocytes and tau pathology was performed.

Results: Our results demonstrated only sparse colocalization of TDP43 and microglia and rare colocalization with astrocytes and tau pathology. This, along with the morphology of the affected cells, which were similar to described multisystem atrophy's typical wizard's hats and flamed-shaped oligodendritic TDP43 inclusions, suggest that the oligodendrocytes could be the mainly affected cells. Further staining is necessary to confirm the presence of TDP43 in oligodendrocytes and neurons.

Conclusions: Several conditions contributed to this man's dementia syndrome including AD, FTLD with TDP43 proteinopathy and hippocampal sclerosis. We suggest that the abnormal combination of pathology in glial cells could specifically contribute to the dementia syndrome.

ALZHEIMER'S DISEASE NEUROPATHOLOGICAL COMORBIDITIES ARE COMMON IN THE YOUNGER-OLD. Malek-Ahmadi M, Intorcchia AJ, Tremblay C, Arce RA, Walker J, Borja CI, Cline MP, Hemmingsen S, Stewart A, Qiji S, Martinez K, Krupp A, McHattie R, Sue LI, Serrano GE, Beach TG. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Clinicopathological studies have demonstrated that Alzheimer's disease dementia (ADD) is often accompanied by clinically undetectable comorbid neurodegenerative and cerebrovascular disease that alter the presence and rate of cognitive decline in aging and ADD. Aside from causing increased variability in clinical response, it is possible that the major ADD comorbidities may not respond to ADD-specific molecular therapeutics. As most reports have focused on comorbidity in the oldest-old, its extent in younger age groups that are more likely to be involved in clinical trials is largely unknown.

Methods: We conducted a survey of neuropathological comorbidities in sporadic ADD using data from the US National Alzheimer's Coordinating Center. Subject data was restricted to those with dementia and meeting National Institute on Aging-Alzheimer's Association (NIA-AA) intermediate or high AD Neuropathological Change (ADNC) levels, excluding those with known autosomal dominant AD-related mutations. Subjects were divided into age-at-death categories for analysis: under 60, 60-69, 70-79, 80-89, 90-99 and 100 or over.

Results: Confirmatory of earlier reports, ADD histopathology is less severe with advancing age, effectively increasing the relative contribution of comorbidities, most of which rise in prevalence with age. Highly prevalent ADD comorbidities are not restricted to the oldest-old but are common even in early-onset ADD. The percentage of cases with ADD as the sole major neuropathological diagnosis is highest in the under-60 group, where "pure" ADD cases are still in the minority at 44%. After this AD as a sole major pathology in ADD declines to roughly 20% in the 70s and beyond. Comorbidity rates for some pathologies, especially LBD, are high even in subjects in their 60s and 70s, at nearly 60%, but for most others, their prevalence increases with age. TDP-43 pathology affects more than 35% of ADD subjects 80 and over while microscopic infarcts reach this rate a decade later. Gross infarcts rise more slowly and affect fewer subjects but still involve 15-20% of ADD after age 80. White matter rarefaction may be underestimated in the NACC database but is present in almost 70% of centenarians with ADD.

Conclusions: Effective clinical trials depend on accurate estimates of required subject numbers, which are dependent on observed effect size and clinical response variability. Comorbidities are likely to affect both, leading to lower probability of clinical trial success. Stratifying ADD clinical trial analyses by presence and types of accompanying comorbidities might identify subgroups with higher effect sizes and greater clinical response rates, but accurate in-vivo diagnostic methods for most comorbidities are still lacking.

CHARACTERIZATION OF ISOLATED HUMAN ASTROCYTES IN AGING AND LEWY BODY DISEASE. Aslama S, Walker JE, Piras IS, Huentelman MS, Arce RA, Tremblay C, Glass MJ, Intorcica AJ, Nelson CM, Suszczewicz KE, Borja CI, Cline MP, Hemmingsen SJ, Qiji SH, Mariner M, Krupp A, Martinez K, McHattie R, Stewart A, Beh ST, Beach TG, Serrano GE. Banner Sun Health Research Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Astrocytes have multiple crucial roles, including maintaining brain homeostasis and synaptic function, phagocytic clearance and response to injury and repair. It has been suggested that astrocyte performance is progressively impaired with aging, leading to imbalances in the brain internal milieu that eventually impact neuronal function and lead to neurodegeneration. Until now the vast majority of evidence of astrocytic dysfunction in aging and Lewy body disease (LBD) has come from experiments done with whole tissue homogenates, astrocytes collected by laser capture or cell cultures derived from animal models or cell lines.

Methods: In this study we conducted an unbiased comparison of human astrocyte gene expression in LBD and control subjects doing whole transcriptome sequencing from enriched human astrocyte populations sorted with anti-GFAP antibodies. Control subjects included both clinically normal subjects (n=8) as well as subjects with non-PD parkinsonism, such as progressive supranuclear palsy (n=7), and dementia Alzheimer's disease (n=10). Cases with LBD included 3 with incidental Lewy body disease (ILBD) and 16 cases of Parkinson's disease (PD) with different disease stages.

Results: Only 3 cases had less than the targeted 40 million reads, while 50% of the cases presented with a substantial number of reads that could not be definitively mapped to either the human or animal genome. We were able to identify hundreds of genes down- or up-regulated in astrocyte enriched cell suspensions from ILBD subjects when compared to advanced PD. Most of the identified genes that are differentially regulated early in disease are related to translation, transcription, and DNA/RNA repair. Another important group of genes that seems to be downregulated are genes associated with cysteine and glutathione redox balance in astrocytes, ion binding proteins, creatine kinase activity, transmembrane signal receptor activity and olfactory receptor activity.

Conclusions: This study supports the hypothesis that astrocytes are affected by Lewy body pathology. We did not observe statistically significant changes in genes implicated in PD, such as SNCA, PARK7, PARK2, LRRK2 and GBA, but we observed changes between ILBD and PD in genes related to function such as translation, transcription, and DNA/RNA repair. As ILBD is a probable prodromal stage of PD, these results suggest astrocytic dysfunction at early stages of a-synuclein pathology. The main unresolved issues include reproducibility in a larger cohort; comparing these results to those obtained with alternative methodology, such as single-nucleus suspensions or laser capture of astrocytes, to determine any differential effects due to modes of tissue processing. At present, there is no "gold standard" for studies like this, but results that replicate between methodologies, would eventually add confidence to these results.

CLINICOPATHOLOGICAL CORRELATION: DOPAMINE AND AMYLOID PET IMAGING WITH NEUROPATHOLOGY IN THREE SUBJECTS CLINICALLY DIAGNOSED WITH ALZHEIMER'S DISEASE OR DEMENTIA WITH LEWY BODIES. Gupta HV, Beach TG, Mehta SH, Shill HA, Driver-Dunckley E, Sabbagh MN, Belden CM, Liebsack C, Dugger BN, Serrano GE, Siderowf A, Pontecorvo MJ, Mintun MA, Joshi AD Adler CH. The University of Kansas Health System; Banner Sun Health Research Institute; Mayo Clinic College of Medicine; Barrow Neurological Institute; Ruovo Clinic; University of California at Davis; University of Pennsylvania; Avid Radiopharmaceuticals; Arizona Alzheimer's Consortium.

Background: Imaging biomarkers have the potential to distinguish between different brain pathologies based on the type of ligand used with PET. AV-45 PET (florbetapir) is selective for the amyloid plaques of Alzheimer's disease (AD) while AV-133 PET is selective for VMAT2, a dopaminergic marker depleted in Parkinson's disease (PD) and dementia with Lewy bodies (DLB). The objective of this study was to report the clinical, AV-133 PET, AV-45 PET, and neuropathological findings of three clinically diagnosed dementia patients who were part of the Avid Radiopharmaceuticals AV133-B03 study as well as the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND).

Methods: Subjects were recruited for the AV133-B03 study, were assessed by neuropsychologists and neurologists, died and had autopsy with neuropathological examination. A total of 3 subjects who had PET imaging with both AV-133 and AV-45 as well as a standardized neuropathological assessment were included. The final clinical, PET scan, and neuropathological diagnoses were compared.

Results: The first subject had a clinical diagnosis of dementia with Lewy bodies (DLB). His AV-133 PET showed bilateral dopaminergic degeneration and AV-45 PET was positive for amyloid. The final diagnosis based on clinical and pathological information was DLB and AD. The second subject was diagnosed clinically with probable AD and AV-45 PET was positive for amyloid while AV-133 PET was normal. Neuropathological diagnostic criteria were met for both DLB and AD. The third subject had a clinical diagnosis of DLB. Her AV-45 PET was positive for amyloid and AV-133 showed dopaminergic degeneration. The final diagnosis based on clinical information and pathology was multiple system atrophy (MSA) and AD.

Conclusions: PET imaging using AV-133 for the measurement of VMAT2 density can help distinguish between AD and DLB. However, some cases of DLB with less-pronounced nigrostriatal dopaminergic neuronal loss can potentially be missed.

DYSREGULATION OF BRAIN INFLAMMATION IN COVID-19, AN AUTOPSY SERIES. Serrano GE, Walker JE, Piras IS, Huentelman MS, Arce RA, Tremblay C, Glass MJ, Sue LI, Intorcica AJ, Nelson CM, Suszczewicz KE, Borja CI, Cline MP, Hemmingsen SJ, Qijia SH, Aslam S, Mariner M, Krupp A, Martinez K, McHattie R, Stewart A, Beh ST, Beach TG. Banner Sun Health Research Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: COVID-19 presents a wide spectrum of clinical manifestations including a systemic hyperinflammatory response. The immune response, although needed for viral elimination, might also contribute to clinical severity. Previous studies have described highly elevated circulating cytokines and an impaired interferon response in severe cases. However, studies of the immune response to COVID-19 are still ongoing. Much less is known about the immune response that takes place in the brain.

Methods: In this study we assessed dysregulation of inflammatory genes and proteins in postmortem brains of subjects that died with COVID-19. We conducted RNA sequencing and immunohistochemistry of microglial Ionized Calcium Binding Adaptor Molecule 1 (IBA1) in two brain regions, olfactory bulb and amygdala. We used brain homogenates of amygdala and blood serum to detect changes of inflammatory proteins using a multiplex protein array.

Results: Our preliminary studies suggest extensive gene expression changes in amygdala and olfactory bulb in subjects who died with COVID-19. We detected similar biological processes enriched in both regions, these included the downregulation of synaptic genes and a modest immune system activation. Some of the changes related to inflammation include upregulation of interferon-related neuroinflammation genes, antiviral enzymes that counteract viral attack, but also Growth Factor Independence-1 (Gfi1) which is a transcriptional repressor protein that plays an important role in suppressing myeloid transformation. Surprisingly, the area occupied by IBA1 immunoreactivity was significantly less in the amygdala of COVID-19 cases; while in olfactory bulb we did not observe any differences when compared to controls. In addition, as expected by prior reports, we found upregulation of inflammation markers in the serum, but downregulation of inflammatory proteins in the amygdala.

Conclusions: These provocative results need further investigation. More work is needed to determine the short and long-term sequelae in survivors of COVID-19, including the evolving immune response to the virus, systemically and within the brain.

GENERATION AND CHARACTERIZATION OF SKIN-DERIVED PRECURSOR CELLS FROM HUMAN AUTOPSY-DERIVED SCALP FIBROBLASTS. Beh ST, Mitchell L, Lue LF, Borja C, Arce R, Intorcchia A, Walker J, Suszczewicz K, Cline M, Hemmingsen S, Qiji S, Krupp A, Martinez K, McHattie R, Stewart A, Mariner M, Tremblay C, Aslam S, Beach T, Serrano G. Banner Sun Health Research Institute; University of Maryland; Arizona Alzheimer's Consortium.

Background: Several cellular and animal models of neurodegenerative diseases have been developed to study the pathological mechanisms or to identify promising drug leads. However, these genetic- or drug-induced experimental models cannot fully develop the neuropathological or clinical phenotypes observed in humans, making it difficult to explore potential underlying mechanisms and effective disease modeling. Human inducible pluripotent stem cells (iPSCs) have been widely used for disease modeling, drug screening, and regenerative therapy. However, iPSCs face limitations due to low efficiency and reprogramming-associated cellular rejuvenation which erases age-associated features for disease modeling. As an alternative approach to iPSC reprogramming, somatic reprogramming allows for the generation of functional human cells that maintain the age-associated features, neuropathological or clinical phenotypes, epigenetic state, and differentiation potential. Human Skin-Derived Precursors (hSKPs) are somatic stem cells and capable of both self-renewal and multipotent differentiation in culture to produce all three primary germ layers. However, hSKPs are rarely reported and the identity of these hSKPs remains ambiguous. In the present study, we aimed to isolate hSKPs from aged human autopsy-derived scalp fibroblasts, and further examined the differentiation potential of hSKPs.

Methods: A human scalp sample (female, >90 years old) was collected at autopsy according to the Western Institutional Research Board approved protocol (WIRB® Protocol #20120821) of the Brain and Body Donation Program of Banner Sun Health Research Institute. The hSKPs were isolated from primary fibroblast culture and examined for the ability to differentiate into various cell lineages. Briefly, mature hSKPs generated from fibroblasts were dissociated into single cells and seeded directly onto chamber slides. Cells were then cultured in an adipogenic, chondrogenic, or osteogenic differentiation medium. After being induced for 28 days, cells were stained with Oil Red-O Solution (for adipocyte differentiation), Alcian Blue Solution (for chondrocyte differentiation), or Alizarin Red Solution (for osteocyte differentiation). The hSKPs characterization and differentiation potential were examined by morphology, immunofluorescence staining, and RT-qPCR.

Results: We successfully isolated hSKPs from aged human autopsy-derived scalp fibroblasts. Positive immunofluorescent reactivities of SOX2 and Nestin are observed in the mature hSKPs. The results of mRNA analysis also showed positive expression of stem cell-specific genes (SOX2, NES, POU5F1, and NANOG) are upregulated in mature hSKPs relative to undifferentiated parental fibroblasts as analyzed by RT-qPCR. In addition, mature hSKPs under multi-inducing conditions were shown to possess multilineage potential, giving rise to fat-, cartilage- and bone-like cells. The results of RT-qPCR analysis also confirmed that the mRNA expression of PPARG, SOX9, and RUNX2 was significantly elevated after being induced for 28 days.

Conclusions: Our results have demonstrated that hSKPs could be isolated from human autopsy-derived scalp fibroblasts initially expanded in monolayer culture and presented properties of self-renew and differentiation potentials. These findings suggest that the hSKPs are an ideal source of stem cells with similar characteristics such as other adult stem cells. Thus fibroblast-derived hSKPs can be a potential clinical source in regenerative medicine. Future studies will explore the capabilities of hSKPs induction into brain cells.

INTERHEMISPHERIC ASYMMETRY IN THE PROGRESSION OF ALZHEIMER-TYPE TAUOPATHY. Tremblay C, Serrano GE, Intorcchia AJ, Walker JE, Arce RA, Curry J, Sue LI, Nelson CM, Glass MJ, Qiji SH, Borja CI, Cline MP, Suszczewicz KE, Hemmingsen SJ, Aslam S, Krupp A, Martinez K, McHattie R, Stewart A, Fleisher AS, Pontecorvo MJ, Atri A, Montine TJ, Chen K, Beach TG. Banner Sun Health Research Institute; Avid Radiopharmaceuticals; Eli Lilly and Company; Brigham and Women's Hospital and Harvard Medical School; Stanford University; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Neurofibrillary tau pathology spread in Alzheimer's disease (AD) mostly shows a stereotypical pattern of topographical progression previously described as the Braak staging system. However, both neuropathological and clinical imaging studies have highlighted the presence of atypical topographic patterns. Moreover, clinical studies suggest that atypical patterns might be associated with interhemispheric asymmetry. As histopathological studies that used bilateral sampling are limited, this study aimed to comprehensively assess interhemispheric tau pathology differences and the presence of topographically atypical cortical spreading patterns.

Methods: Immunohistochemical staining for detection of tau pathology was performed in 23 regions of interest bilaterally in 57 autopsy cases. Tau pathology density was semi-quantitatively assessed and compared between cortical regions and hemispheres.

Results: Frequent mild (82% of cases) and occasional moderate (32%) interhemispheric density discrepancies were observed while marked discrepancies were uncommon (7%) and restricted to occipital regions. Left and right hemispheric tau pathology dominance was observed with similar frequencies, except in Braak stage VI that favored a left dominance. Interhemispheric Braak stage differences were observed in 16% of cases and were more frequent in advanced (IV-VI) than early stages (I-III). One atypical lobar topographical pattern, the "early occipital pattern", where occipital tau pathology density exceeded frontal lobe score, was identified in 4 cases (7%), favoring a left dominant asymmetry.

Conclusions: We speculate that asymmetry and atypical topographical progression patterns may be associated with described atypical AD clinical presentations and progression characteristics, which should be tested by comprehensive clinicopathological correlations.

LONG-TERM STORAGE EFFECTS ON P-TDP43 IMMUNOHISTOCHEMICAL AND HISTOCHEMICAL NEURODEGENERATIVE DIAGNOSTIC STAINING OF ARCHIVED PARAFFIN SECTIONS. Intorcía AJ, Tremblay C, Arce RA, Walker J, Borja CI, Cline MP, Hemmingsen S, Stewart A, Qiji S, Martinez K, Krupp A, McHattie R, Sue LI, Beach TG, Serrano GE. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: It is a common practice in histology laboratories to store wet fixed tissue or take extra sections at the time of sectioning and store them for possible future usage. There has long been conjecture about whether long-term storage might alter the staining properties of such tissue, but not many studies confirm such effects. In this study we compared the staining for phosphorylated TDP-43 (p-TDP) in brain tissue that had been stored at room temperature for years either as wet fixed tissue in buffer, embedded in paraffin and sections collected years before this study.

Methods: Wet fixed tissue from 15 p-TDP positive cases were dissected and embedded at the same area of the original block. Paraffin sections were cut days before the staining from both the original block and newly dissected one. In addition we stained paraffin slides that were cut and stored for year. All sections were stained with a commercial p-TDP (CosmoBio Ser409/410) and with a polyclonal antibody for p-TDP that was privately obtained from Dr. H. Akiyama, Tokyo, Japan. The methods used were identical except for the usage of differing epitope exposure methods: 10 minutes in boiling 0.1 M sodium citrate followed by 3 minutes in 80% formic acid for the commercial p-TDP or 30 minutes in boiling 0.1 M sodium citrate for the privately obtained p-TDP. Primary antibody concentrations were 1:10,000 for both antibodies.

Results: Initial results of blinded semi-quantitation of staining density suggests that both long term storage of either wet fixed tissue or cut sections reduced p-TDP immunoreactivity. We have not observed similar effects with other common neurodegenerative disease pathological targets such as tau (AT8), amyloid (6E10) and p- α -synuclein.

Conclusions: Most pathological protein and peptide aggregates in stored tissue sections may be suitable for study even after prolonged storage, this should be avoided for p-TDP-43.

NEUROPATHOLOGICAL DIAGNOSES OF SUBJECTS AUTOPSIED IN THE PHASE 3 CLINICOPATHOLOGICAL STUDY OF FLORTAUCIPIR F18 PET IMAGING. Beach TG, Montine TJ, Serrano GE, Sue LI, Intorcchia AJ, Walker JE, Glass M, Tremblay C, Arce R, Suszczewicz K, Borja C, Cline M, Qiji S, Hemmingsen S, Stewart A, Martinez K, Krupp A, McHattie R, Beh ST, Aslam S, Mariner M, Fleisher AS, Pontecorvo MJ, Devous Sr. MD, Lu M, Mintun MA, on behalf of the A16 study investigators. Banner Sun Health Research Institute; Stanford University School of Medicine; Avid Radiopharmaceuticals; Arizona Alzheimer's Consortium.

Background: Avid Radiopharmaceuticals conducted a prospective case-control clinicopathological study of flortaucipir F18 PET Imaging (AV-1451-A16) from October 2015 through June 2018. Sixty-seven valid study autopsies were performed. The cerebral patterns of flortaucipir PET images were visually assessed and compared to the patterns of immunohistochemical tau pathology. The study met pre-specified success criteria, with imaging predicting an NIA-AA B3 level of tau pathology (Braak V/VI) and a high level of Alzheimer's disease neuropathologic change.

Methods: This presentation is an initial report of the detailed neuropathological diagnoses of the 67 primary study subjects. There were 35 females and 32 males, mean age 82.6 (SD 9.4). Fifty-three cases met intermediate or high ADNC levels, consistent with AD as a cause of cognitive impairment. Standardized neuropathological examinations were performed on all subjects.

Results: Many subjects had additional major neuropathological findings (not mutually exclusive), meeting neuropathological diagnostic criteria of dementia with Lewy bodies (DLB; n=7), Parkinson's disease (PD; n=1), progressive supranuclear palsy (PSP; n=5), hippocampal sclerosis (HS; n=5), vascular dementia (n=3) and corticobasal degeneration (CBD; n=1), while others had lesser findings of TDP-43 proteinopathy restricted to the mesial temporal lobe (n=19), Lewy body pathology not meeting criteria for DLB or PD (n=18), age-related tau astroglialopathy (ARTAG; n=15) or remote cerebral infarcts (n=10). Cases with less than intermediate ADNC (n=14) met neuropathological diagnostic criteria (not mutually exclusive) for PD (n=2), HS (n=2), DLB (n=1), PSP (n=1), CBD (n=1) and others had additional neuropathological findings of TDP-43 proteinopathy restricted to the mesial temporal lobe (n=2), Lewy body pathology not meeting criteria for DLB or PD (n=4), ARTAG (n=3) or remote cerebral infarcts (n=2).

Conclusions: This high proportion of mixed neuropathology is typical of what has been published for other elderly autopsied subjects. Correlations of flortaucipir F18 PET imaging with these varied neuropathological types will be undertaken.

OLFACTORY BULB DEAFFERENTATION IN SUBJECTS DYING WITH COVID-19. Tremblay C, Intorcchia AJ, Walker JE, Arce RA, Borja CI, Suszczewicz KE, Cline MP, Hemmingsen SJ, Qiji SH, Sue LI, Nelson CM, Aslam S, Mariner M, Krupp A, Martinez K, McHattie R, Stewart A, Beh ST, Beach TG, Serrano GE. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: There have been clinical descriptions of diverse neurological effects in COVID-19 disease, involving up to 36% of patients. It appears likely that most of these are not caused by viral brain invasion but by systemic accompaniments of critical illness such as coagulopathy, deleteriously upregulated immune response, autoimmune mechanisms, hypoxia or multiorgan failure. Anosmia or hyposmia is present in a majority of COVID-19 patients, and there is early and severe involvement of the nasopharyngeal mucosa and olfactory epithelium. Preliminary studies by our group have found substantial gene expression changes in olfactory bulb (OB) in COVID-19 patients when compared to control. However, only few genes were differentially expressed in subjects with detectable SARS-CoV-2 RNA when compared with COVID-19 patients with no detectable SARS-CoV-2 RNA in the OB. As spontaneous discharge of olfactory epithelial afferents dictates intra-olfactory bulb neurophysiological activity and connectivity, we hypothesized that olfactory bulb deafferentation during COVID-19 is responsible for a large fraction of our observed olfactory bulb transcriptional changes.

Methods: As the olfactory marker protein (OMP-1) is a specific marker of olfactory epithelial afferents to the olfactory bulb and is severely depleted in animal model lesions of olfactory epithelium, we quantified OMP-1-immunoreactivity in the olfactory bulb of subjects dying with or without COVID-19. Additionally, we quantified olfactory bulb tyrosine hydroxylase (TH), which is often also reduced after olfactory epithelium lesions, and SNAP-25, a pan-synaptic marker.

Results: COVID-19 cases (n = 18) were generally elderly and were not significantly different in age or gender distribution from the non-COVID-19 cases (n = 28). Both COVID-19 and non-COVID-19 cases had a wide range of neuropathological diagnoses. The area occupied by OMP-1 immunoreactivity in COVID-19 cases was significantly less, about 60% of that in control cases but amongst subjects with COVID-19, there was no significant difference between OBT-SARS-CoV-2-PCR-positive and negative cases. There were no significant group differences for TH or SNAP-25, supporting a selective effect for OMP-1.

Conclusions: We suggest that olfactory dysfunction, and some of the COVID-19-associated transcriptional changes that we have reported for the olfactory bulb and amygdala, may be due to olfactory bulb deafferentation and subsequent transsynaptic effects. Additionally, animal models of olfactory bulb deafferentation or bulbectomy indicate a possibility for widespread changes in interconnected brain regions, providing a possible substrate for diverse post-acute COVID-19 neurological sequelae.

OLFACTORY BULB PATHOLOGY AND ITS INFLUENCE ON OLFACTORY FUNCTION IN AGING. Tremblay C, Intorcica AJ, Walker JE, Arce RA, Qiji SH, Borja CI, Cline MP, Suszczewicz KE, Hemmingsen SJ, Aslam S, Mariner M, Krupp A, Martinez K, McHattie R, Stewart A, Beh ST, Sue LI, Wilson JR, Adler CH, Shill HA, Driver-Dunckley E, Mehta SH, Serrano GE, Beach TG. Banner Sun Health Research Institute; Arizona State University; Mayo Clinic Arizona; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Decline of olfactory function is frequently observed in aging and is an early symptom of neurodegenerative diseases. As the olfactory bulb (OB) is one of the first regions involved by pathology and may represent an early disease stage, we specifically aimed to evaluate the contribution of OB pathology to olfactory decline in cognitively normal aged individuals without parkinsonism or dementia.

Methods: This clinicopathological study correlates OB tau, amyloid β ($A\beta$) and α -synuclein (α Syn) pathology densities and whole brain pathology load to olfactory identification function as measured with the University of Pennsylvania Smell Identification Test (UPSIT) and clinical data measured proximate to death in a large autopsy study including 138 cases considered non demented controls during life.

Results: Tau pathology was frequently observed in the OB (95% of cases), while both $A\beta$ (27% of cases) and α Syn (20% of cases) OB pathologies were less commonly observed. A weak correlation was only observed between OB tau and olfactory performance, but when controlled for age, neither OB tau, $A\beta$ or α Syn significantly predict olfactory performance. Moreover, whole brain tau and α Syn pathology loads predicted olfactory performance, however only α Syn pathology loads survived age correction.

Conclusions: In conclusion, OB tau pathology is frequently observed in normally aging individuals and increases with age but does not appear to independently contribute to age-related olfactory impairment. Results suggest that further involvement of the brain seems necessary to contribute to age-related olfactory decline.

PATIENT-BASED POSTMORTEM FIBROBLAST BANKING FOR AGE-RELATED NEURODEGENERATIVE DISEASE RESEARCH. Beh ST, Lue LF, Brafman DA, Frisch C, Churko J, Arce R, Borja C, Intorcio A, Walker J, Suszczewicz K, Cline M, Hemmingsen S, Qiji S, Krupp A, Martinez K, McHattie R, Stewart A, Mariner M, Tremblay C, Aslam S, Beach T, Serrano G. Banner Sun Health Research Institute; Arizona State University; University of Arizona; Arizona Alzheimer's Consortium.

Background: The Brain and Body Donation Program (BBDP) at the Banner Sun Health Research Institute (BSHRI) annually banks postmortem tissues from 60-90 autopsy cases who were non-demented elderly or had neurological disorders. The Human Cells Core for Translational Research (HCCTR), established in 2018, takes advantage of the BBDP tissue resource to build a human fibroblast banking program using postmortem scalp tissues. Fibroblasts are widely used for inducible pluripotent stem cell reprogramming and differentiation. The purpose of banking postmortem fibroblasts from clinically and neuropathologically characterized patients is to provide human cells to academic and pharmaceutical communities to facilitate translational research and drug development for age-related diseases that are currently without a cure.

Methods: Postmortem human scalp tissues from BBDP donors have been routinely used to obtain fibroblasts by direct culturing of scalp explants. Dermal tissues were rinsed, chopped into 1-mm³ pieces, and placed in 6-well plates for explant cultures in a 37°C incubator with 5% CO₂. Cells were harvested when they reached 80-90% confluence and expanded in T75 culture flasks at 1:2 ratios. Confluent passage-3 cells were harvested, counted, and resuspended in cryoprotectant. Cryoprotected cell aliquots were stored in the vapor phase inside a liquid nitrogen tank. The viability of the cells from cryopreservation was evaluated by hemocytometer counting of trypan blue dye-excluded cells. All banked passage-3 cells were routinely characterized by a set of proteins and genes [vimentin, fibronectin, fibroblast-specific protein 1 (FSP), fibroblast activation protein (FAP), alpha-smooth muscle actin (α -SMA), and Thy-1 cell surface antigen] that have a cellular property and functional significance to the fibroblasts by immunofluorescence staining and qPCR. Commercially available primary fibroblasts and keratinocytes served as positive and negative cell-type controls, respectively. The apolipoprotein E (APOE) genotype was determined by qPCR techniques. A non-integrating Sendai viral approach was used to generate human-induced pluripotent stem cells (hiPSCs) from one of the established patient fibroblast lines. Several clones were isolated and subjected to detailed phenotypic characterization.

Results: Currently, we have banked cryoprotected fibroblasts from 85 cases of different ages, APOE genotypes, and disease diagnoses. The postmortem fibroblasts maintained high cell viability (90-95%) during cryo-storage. Positive immunofluorescent reactivities of FSP, FAP, fibronectin, α -SMA and vimentin are observed in the banked passage-3 fibroblasts. The results of mRNA analysis also showed positive expression of FAP, vimentin, fibronectin, and Thy-1 cell surface antigen. Fibroblasts from our culture were negative for cytokeratin in both immunofluorescence and RT-qPCR assay. We also demonstrated that the banked fibroblasts from a postmortem elderly donor were successfully reprogrammed to hiPSCs.

Conclusions: Our results have demonstrated the feasibility of routine banking of patient scalp-derived fibroblasts. The cells exhibited protein and gene expression profiles similar to commercially available primary fibroblasts and maintained high viability in cryoprotectant. Long-term efforts in this cell banking program will result in a valuable human cell resource to use for a better understanding of normal aging and age-related neurodegenerative diseases. The cryogenically preserved cells are available for request at the program website of the BSHRI.

SEX DIFFERENCES IN ALZHEIMER'S DISEASE: MOLECULAR PATHWAY FOR SYNAPTIC LOSS. Walker JE, Qiji S, Stewart A, Biddle B, Mesch K, Mitchell L, Tremblay C, Intorcchia A, Arce R, Suszczewicz K, Borja C, Cline M, Hemmingsen S, Martinez K, Krupp A, McHattie R, Aslam S, Mariner M, Beh ST, Beach TG, Serrano GE. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Multiple studies have suggested that females are affected by Alzheimer's Disease (AD) more severely than males. Our previous studies have shown that females with AD are more likely to progress to severe cognitive dysfunction and have a greater proportional loss of brain weight. Additional experimentation with enzyme-linked immunosorbent assays (ELISA) revealed that pre-synaptic protein SNAP25 in both the frontal and temporal cortex was significantly reduced in females with AD but not males, suggesting that the sex differences in AD brain weight loss may be largely due to synaptic terminal loss. For this study, we wanted to further investigate possible molecular pathways involved in AD synaptic loss.

Methods: Subjects were volunteers as part of the Brain and Body Donation Program (BBDP) at the Banner Sun Health Research Institute in the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND). Subjects for the current study (N=93) were chosen by searching the BBDP database for cases with a clinicopathological diagnosis of AD (N=49) or control (N=44) from both genders. Control cases were chosen based on the absence of dementia with no or low AD pathology. AD cases were selected based on meeting criteria for clinical dementia and end-stage AD pathology (ADD). Gray matter from frozen frontal cortex was dissected for protein and RNA isolation. Molecular pathways related to synaptic pruning were explored using qPCR and Taqman Gene Expression Assays. All assays were validated with $r^2 > 0.9$ and PCR efficiency was calculated and determined to be between 90-110%. Quantification of GFAP protein was done using commercially prepared ELISA.

Results: There were significant differences in several genes that were analyzed when comparing AD vs ND and males to females. Synaptophysin was upregulated in male AD (Male ND vs. AD $p=.005$), as well as VAMP2 (Male ND vs. AD $p=.01$), CHRM3 (Male ND vs. AD $p<.0001$), and 5HTR2 (Male ND vs. AD $p<.0001$) which are genes relating to synaptic vesicle release and neurotransmitter receptors, but there were no significant differences between females ND vs AD. Genes associated with glia mediated synaptic pruning were upregulated in females, most notable were complement gene C5 (Female ND vs. AD $p=.02$) and astrocyte-associated Megf10 (Female ND vs. AD $p=.0001$) but this was not significant in males. GFAP protein expression was significantly elevated in AD; but there were not convincing differences between males and females.

Conclusions: Several genes for synapses (VAMP2, SYP) and neurotransmitters (GRIN1, CHRM3, 5HTR2) were upregulated in AD even though it is well established in the literature that synaptic proteins and neurotransmitters are severely decreased in AD. We hypothesize that the observed increase in gene expression could be compensatory for the known reduction of proteins. This increase was only significant between males, implying that they may be able to better mitigate synaptic loss than females. Genes that play a key role in synaptic pruning were upregulated in AD overall, but significant only in females (C5, Megf10) which may indicate a higher immune response to the disease which could be deleterious. The combination of increased inflammatory genes in females and an inability to compensate as well by increasing expression of synapses and neurotransmitters may explain why females have a greater loss of synaptic density.

THE EFFECT OF AGING AND NEUROLOGICAL DISORDERS ON MUSCLE FIBER SIZE IN THE PSOAS MUSCLE: A PILOT STUDY. Arce R, Beh ST, Intorcchia A, Walker JE, Suszczewicz KE, Borja CI, Cline MP, Hemmingsen SJ, Qiji SH, Aslam S, Mariner M, Krupp A, Martinez K, McHattie R, Stewart A, Tremblay C, Beach TG, Serrano GE. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Loss of muscle mass, termed sarcopenia, is common in aging and in neurological disorders of aging such as Alzheimer's and Parkinson's diseases, and may affect mobility and performance of daily tasks. It is unknown how these neurological disorders affect the skeletal muscle fiber composition in comparison with normal aging, and how muscles adapt to movement impairment caused by neurological diseases. The purpose of this study was to analyze type 1 and type 2 fibers in the psoas muscle of aging individuals with and without neurodegenerative disorders to gain insight into age and disease-related sarcopenia.

Methods: Psoas muscle was collected at autopsy from human subjects that were part of the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) and Brain and Body Donation Program (BBDP). Subject selection was based on clinicopathological diagnoses of Parkinson's disease, Alzheimer's disease, progressive supranuclear palsy, and Controls. A longitudinal and cross-sectional portion of the psoas muscle was dissected at autopsy at the level of the L5 of the spinal column and fixed in neutral buffered formalin for two days, then changed to 50% ethanol. Samples were then paraffin-embedded, cut at 6 microns, and mounted on histological slides. Anti-fast and anti-slow myosin heavy chain unconjugated antibodies diluted at 1:3000 with a 97°C sodium citrate antigen retrieval step were used to identify Type I and Type II muscle fiber types. Each section was photographed in three representative areas following staining and a Zeiss AxioVision software was used to determine mean fiber cross-sectional areas.

Results: The group age means were not significantly different, with all groups having a mean of 82 years. Muscle fiber size means for untyped fibers had considerable variation; AD muscle fiber means were smaller than those of controls while PD and PSP means were larger. Type I fibers were similar in the diagnostic groups while Type II fibers were significantly smaller in AD. For PD and PSP, Type II fiber size means were larger than those of controls.

Conclusions: This pilot study showed that Type II muscle fibers may be atrophied in AD but hypertrophied in PD and PSP. Tissue atrophy may explain the findings for AD. For PD and PSP, we hypothesize that tremor and other involuntary muscle movements may induce hypertrophy. Expanding this study to larger subject numbers may provide insight as to how neurological disorders affect skeletal muscles.



Arizona Alzheimer's Consortium 23rd Annual Scientific Conference

Additional Abstracts

A COST-EFFECTIVE MULTI-MODALITY MACHINE LEARNING FRAMEWORK FOR PREDICTION OF ALZHEIMER' DISEASE. Zheng Z, Su Y, Chen K, Weidman D, Wu T, Lo S-C, Lure F, Li J. Georgia Institute of Technology; Banner Alzheimer's Institute; Arizona State University; MS Technologies Corp; Arizona Alzheimer's Consortium.

Background: Early prediction of the AD risk for individuals with MCI has important clinical value. Machine Learning (ML) models integrating multi-modality neuroimaging datasets have shown great promise. The acquisition costs of different data modalities vary significantly. It is not cost-effective to require all patients to acquire all data modalities. We proposed a data-efficient ML framework, namely the Uncertainty-driven Modality Selection (UMoS) framework, to sequentially add modalities for each patient on an as-needed basis while at the same time ensuring high diagnostic/prognostic accuracy.

Methods: The dataset included 1319 T1-MRI scans from MCI patients in ADNI and among these 612 additionally had amyloid-PET. Regional volumetric and thickness measures were computed using FreeSurfer v7.1 from MRI and regional SUVR measures were computed using our in-house pipeline from amyloid-PET. MRI is used in the standard of care while amyloid-PET has less accessibility and is more expensive. Thus, the goal of UMoS was to save a patient from needing PET if doing so did not hurt prediction accuracy. To achieve this, we first trained two elastic net logistic regression models to predict the risk of conversion to AD for MCI patients: one with MRI only; the other one additionally including amyloid-PET. Uncertainty quantification (UQ) was performed to quantify the predictive uncertainty of the MRI model. Under the UMoS framework, each individual was first predicted using the MRI model. If the predictive uncertainty was high, the individual would be predicted using the MRI+PET model. The uncertainty threshold was selected by balancing the saving of PET in the patient cohort and the prediction accuracy.

Results: Under 10-fold cross-validation, UMoS achieves 0.851 AUC (0.782/0.809 sensitivity/specificity using 0.5 probability cutoff), with 46.7% of patients predicted by the MRI model and 53.3% by the MRI+PET model. If the MRI +PET model is used to predict all patients, the performances are 0.873 AUC (0.776/0.811 sensitivity/specificity).

Conclusions: We proposed an ML framework, UMoS, that used predictive uncertainty of the MRI model to drive the decision if less-accessible amyloid-PET was needed for predicting MCI conversion to AD. This framework allows an individualized approach to make accurate predictions based on available data and leverage additional data only when necessary. With the UMoS framework, we achieve prediction performance at a similar level to the model that needs both MRI and PET for predicting MRI progression to AD, but UMoS saves 46.7% of patients from needing PET.

A NEW FLORTAUCIPIR PET BIOMARKER BASED ON GRAPH THEORY APPLIED TO FORMER AMERICAN FOOTBALL PLAYERS. Protas H, Su Y, Luo J, Chen K, Alosco ML, Adler CH, Balcer LJ, Bernick C, Au R, Banks SJ, Barr WB, Coleman MJ, Dodick DW, Katz DI, Marek KL, Mariani ML, McClean MD, McKee AC, Mez J, Palmisano JN, Peskind ER, Turner RW, Wethe JV, Rabinovici G, Johnson K, Tripodis Y, Cummings JL, Shenton ME, Stern RA, Reiman EM, for the DIAGNOSE CTE Research Project. Banner Alzheimer's Institute; Arizona State University; Boston University; Mayo Clinic, Scottsdale; NYU Langone Health; Lou Ruvo Center for Brain Health, Cleveland Clinic; University of Washington; University of California, San Diego; Brigham and Women's Hospital; Invicro, LLC; VA Puget Sound Health Care System; George Washington University; University of California, San Francisco; Harvard Medical School; University of Nevada; University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease that is characterized by perivascular foci of phosphorylated tau (p-tau) notably in the depths of sulci, with varying patterns in the cerebral cortex. Prior studies show elevated flortaucipir (FTP) PET binding in former American professional football players (PRO). However, the association of p-tau with clinical measures remains unclear using regional FTP SUVR as early signs of CTE related tau pathology. Graph theory (GT) takes advantages of the spatial variability in p-tau load and allows the integration of regional measures to define GT based measures. Here we examine the GT based measures in two CTE cohorts to evaluate their utility in assessing p-tau related pathology in CTE.

Methods: The graph procedure was optimized in FTP PET images in a group of 26 PRO with reported cognitive and/or behavioral symptoms and 30 asymptomatic controls without a history of traumatic brain injury (the DETECT Study) and identified the GT measure, entorhinal tau strength, as the target metric with the best group separation between PRO and controls. The optimized graph procedures were then applied to the DIAGNOSE CTE Research Project dataset (99 former PRO, 51 former college football players [COL], and 52 controls without exposure to repetitive head impacts [CTL]) and we examined entorhinal tau strength's ability to differentiate the exposure groups and relationship to consensus-based diagnoses of Traumatic Encephalopathy Syndrome (TES), the clinical syndrome associated with CTE.

Results: Entorhinal tau strength was significantly different among the three exposure groups ($p=0.0001$) similar to regional SUVR measures. Regional SUVR did not differentiate players (PRO+COL) with and without TES, while entorhinal tau strength approached although did not reach significance. Entorhinal tau strength is the only FTP measure that showed significant differences ($p=0.006$) between those players with cognitive impairment and players without.

Conclusions: While there is still considerable overlap in between-group measurements, GT based entorhinal tau strength, is potentially more sensitive in detecting tau changes in players with and without TES. Additional studies are necessary to clarify the value of this new measure in detecting underlying CTE pathology.

ADDRESSING IMAGING ACCESSIBILITY BY CROSS-MODALITY TRANSFER LEARNING.

Zheng Z, Su Y, Chen K, Weidman D, Wu T, Lo S-C, Lure F, Li J. Georgia Institute of Technology; Banner Alzheimer's Institute; Arizona State University; MS Technologies Corp; Arizona Alzheimer's Consortium.

Background: Multi-modality images including magnetic resonance imaging (MRI) and positron emission tomography (PET) are employed in Alzheimer's Disease research and clinical applications, which provide complementary and overlapping information and have different levels of accessibility. Transfer learning as a deep learning approach has the capability to transfer the trained information between modalities and datasets which may allow accurate diagnosis/prognosis with only the more accessible modalities. We investigate a Cross-Modality Transfer Learning (CMTL) approach in this study.

Methods: This study included 936 MCI participants from ADNI who have MRI, with 213 of them converting to AD in 36 months—namely converters (CON), while the remaining subjects are considered as non-converters (N-CON). Among these participants, 49 also have tau-PET (13 CON and 36 N-CON). 67 AD and 393 normal controls (NC) who have tau-PET were also included. PET images were processed by the ADNI PET core to generate regional standardized uptake value ratio (SUVR) with inferior cerebellum referencing including 84 cortical and sub-cortical SUVR features used in this study. T1-weighted MRI were processed in-house using FreeSurfer v7.1, and 194 regional thickness and volumetric features were included. In addition to imaging features, sex, age, education, MMSE score, and ADAS score were also included in this study. The CMTL approach is implemented as the following. A teacher model was initially trained using only tau-PET features with a feed-forward neural network architecture for the AD vs NC classification task and subsequently applied to the MCI participants to differentiate CON from N-CON. A student model is trained using MRI features only with the same model architecture for the same task. To achieve knowledge distillation (KD), the student model is refined by additional model training which encourages the outputs of the same layer from the student model to be similar to the outputs from the teacher model.

Results: Based on 50 times random training-test split of the dataset, the student model without KD has, on average, 0.668 sensitivity and 0.841 specificity on the test set in the prediction of MCI conversion (43 CON and 139 N-CON in the test set). Using CMCT, the sensitivity improved to 0.702 ($p=0.036$), while the specificity has no significant change.

Conclusions: We proposed a CMCT model that allows the transfer of knowledge learned from the more expensive and less accessible tau-PET and allows improved diagnosis/prognosis accuracy using MRI images only compared to models trained using MRI data alone.

ASSOCIATION BETWEEN COVID-19 LOCKDOWN POLICIES IN ASSISTED LIVING FACILITIES AND LONELINESS AMONG RESIDENTS WHO LIVE WITH ALZHEIMER'S DISEASE AND RELATED DEMENTIAS: A RAPID REVIEW. Manis DR, Peckham A. Arizona State University; McMaster University; University of Toronto; Arizona Alzheimer's Consortium.

Background: Assisted living facilities are congregate care homes that provide support for activities of daily living and health and social care services. Nearly half of the older adults who reside in assisted living facilities live with physician-diagnosed Alzheimer's disease and related dementias (ADRD). During the COVID-19 pandemic, assisted living facilities were subject to the same lockdown policies that were implemented in nursing homes to curtail the spread of COVID-19. In this study, we review the literature on the association between lockdown policies in assisted living facilities and loneliness among residents who live with an ADRD diagnosis.

Methods: We conducted a rapid review that examined lockdown policies in assisted living facilities and loneliness among residents who live with an ADRD. We searched Medline, Embase, and PsychInfo (via Ovid) for original research or knowledge syntheses in English from January 2020 to August 2022. We searched titles and abstracts for the terms "assisted living," "retirement homes," "social isolation," "loneliness," "caregivers," and "visits." We additionally reviewed reference lists for potentially relevant studies, and we included studies identified by other experts not captured in our search. We included articles assessing the impact of COVID-19 lockdowns on psychosocial measures (e.g., loneliness, depression, mood, quality of life, etc.) for residents living with an ADRD in either an assisted living facility, retirement home, or skilled nursing facility. We excluded conference publications, protocols, and gray literature. Two reviewers screened all potentially relevant articles; in cases of disagreement, consensus was reached through discussion. As this is a rapid review, we did not conduct a quality appraisal of the included articles. We summarized the characteristics of the included articles and narratively synthesized the results.

Results: We identified 36 articles from database searching, of which 11 were duplicates (n=25). After title and abstract screening, 10 articles underwent full-text review (n=10). We included seven articles in our review and identified two additional articles through our review of reference lists and discussion with other experts (n=9). Synthesized articles were published in either 2021 (n=5) or 2022 (n=4). Original research articles were conducted in Italy (n=1), France (n=3), USA (n=2), and South Africa (n=1). Five studies used a quantitative design (n=5), two studies used a qualitative design (n=2), and two systematic reviews were included (n=2). Lockdown and visitor restriction policies in assisted living facilities consistently resulted in increased depression, anxiety, and loneliness among residents living with ADRD. The implementation of videoconferencing technologies to maintain contact with caregiver partners and create inclusive communities may be an effective intervention for reducing the negative psychosocial effects associated with lockdown and visitor restriction policies.

Conclusions: Lockdown and visitor restriction policies in assisted living facilities increased feelings of loneliness, depression, and isolation among residents living with ADRD. The use of videoconferencing technologies to regularly connect with family, friends, and other residents may counteract the negative psychosocial consequences of these policies. Our findings contribute to on-going policy discussions for mitigating the spread of COVID-19 and other febrile respiratory illnesses in congregate care homes while balancing the needs of vulnerable older adults who live with ADRD and their need for contact with their caregiver partners.

ASSOCIATION OF AGE WITH GRAY TO WHITE MATTER CONTRAST DIFFERENCES IS MEDIATED BY WHITE MATTER INTEGRITY IN HEALTHY OLDER ADULTS. Smith SG, Bharadwaj PK, Van Etten EJ, Hishaw GA, Trouard TP, Alexander GE. University of Arizona; Arizona Alzheimer's Consortium.

Background: Gray to white matter contrast (GWC) measured by structural T1 magnetic resonance imaging (MRI) has shown age-related differences associated with healthy and pathological aging in older adults, with frontal and temporal regions preferentially affected. These contrast effects are thought to reflect MR white matter signal differences, but the underlying neurobiological mechanisms remain unclear. We sought to examine if measures of global white matter integrity assessed by diffusion tensor imaging (DTI) have a role in mediating the relationship between age and regional lobar GWC in healthy aging.

Methods: A cohort of 163 healthy adults ages 50 to 89 (mean±sd age = 69.7±10.4, 81F/82M, mean±sd Mini-Mental State Exam = 29±1.2) were included. Volumetric T1 and diffusion-weighted 3T MRI scans were processed using FreeSurfer (v5.3) and TRACULA (Tracts Constrained by Underlying Anatomy; Yendiki et al., 2011) to compute average global whole brain estimates of fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) from 18 major white matter tracts. GWC was computed using FreeSurfer for 68 regions of interest for each participant, which were averaged to create frontal, temporal, parietal, and occipital lobe values. Lobar white matter hyperintensity (WMH) volumes were obtained with T1 and T2 FLAIR scans using the lesion segmentation toolbox (Schmidt et al., 2012) with SPM12. Mediation analyses were conducted with SPSS PROCESS macro software (Hayes, 2012), including percentile bootstrap resampling with 10,000 iterations to provide 95% confidence intervals.

Results: After controlling for sex, hypertension status, and corresponding lobar WMH volume, analyses showed significant direct effects of age with greater age associated with decreased GWC in frontal, parietal, temporal (p 's <.001), and occipital (p < .05) lobes. Further, global MD (-.01 (SE=.006), 95% CI, [-.03, -.001]) and RD (-.01 (SE=.006), 95% CI, [-.02, -.002]), but not AD, partially mediated the age effects on GWC with older age associated with greater MD and RD, which in turn was associated with only lower frontal GWC. Including the same covariates, FA (-.01 (SE=.04), 95% CI, [-.02, -.001]) partially mediated the effect of age only on temporal GWC, such that older age was associated with lower FA, which in turn was associated with lower temporal GWC.

Conclusions: In a sample of healthy older adults, we found that increasing age was associated with less GWC in frontal, temporal, parietal and occipital lobes. Global DTI white matter integrity metrics partially mediated the relation of age to lobar GWC, but only in the frontal and temporal lobes, after we controlled for vascular risk factors of hypertension and WMH volume. Together, our findings suggest that age-related degradation of myelin and reductions in directional white matter integrity may reflect underlying factors contributing to differences in GWC with increasing age for regions preferentially vulnerable to brain aging, such as the frontal and temporal lobes. Future work is needed to further evaluate how regional GWC differences influence the progression toward healthy versus pathological aging.

CHARACTERIZATION OF COGNITIVE FUNCTION AND AMYLOID BETA IN A HUMANIZED APOE ALZHEIMER'S DISEASE MOUSE MODEL. Altemus J, Cortes-Flores H, Wiegand JP, Brinton RD. University of Arizona; Arizona Alzheimer's Consortium.

Background: APOEε4 is the greatest genetic risk factor for late onset Alzheimer's Disease (LOAD). The product of this gene, apolipoprotein E isoform ε4, has been characterized as a lipid transporter and many of its receptors and mechanisms have been identified. Studies have shown that APOEε4 exacerbates accumulation of Aβ peptides and correlates with a decline in cognitive function in humans. We investigated the translational feasibility of the humanized APOE3 (JAX #029018) and APOE4 (JAX #027894) mouse model on two hallmark pathologies of LOAD: cognitive decline and b-amyloid (Aβ) generation in brain.

Methods: Novel object recognition (NOR), open field (OF), and CatWalk analyses were conducted in 18 month old transgenic mice with humanized APOEε3 homozygous (B6(SJL)-ApoEtm1.1(APOE*3)Aduij/J), APOEε3/4, or APOEε4 homozygous genes (B6(SJL)-ApoEtm1.1(APOE*4)Aduij/J). NOR analyses included discrimination index, OF center zone time, whereas CatWalk included mobility measures including cadence and speed. Aβ38, Aβ40, and Aβ42 analyses were assessed in brain and plasma.

Results: A sex difference was seen in plasma amyloid levels with females having lower Aβ40, Aβ42, and Aβ42/40, specifically hAPOEε3/3 females when analyzed by genotype + sex. The sex difference was not evident in hippocampal amyloid levels, indicating that the role of sex in modulating amyloid levels may be specific to peripheral effects. Interestingly, hippocampal Aβ42 was lower in hAPOEε3/4 mice vs hAPOEε3/3 and hAPOEε4/4 mice, suggesting a potential neuroprotective effect in heterozygous mice. Hippocampal Aβ40 and Aβ42/40 ratios were not different across genotype or sex, and Aβ38 was not detected in any group. OF mean speed was lower in hAPOEε3/4 mice vs hAPOEε4/4 mice, while OF center zone time showed no differences across groups. NOR analyses and motor function analyses indicated no differences across genotype or sex. Male vs female analyses were performed using two-sided t-tests, while all other analyses were performed using one way ANOVA.

Conclusions: Differential peripheral and brain Aβ levels across genotype and sex suggest potential translational applicability in 18-month (human age equivalent ~56 years) APOE mice. While this distribution generally resembles that of a heterogeneous human population, this age point may be too early to detect cognitive and motor changes in this mouse model.

CLINICOPATHOLOGICAL CORRELATES OF RAPIDLY PROGRESSIVE ALZHEIMER'S DISEASE. Alexander R, Atri A, Malek-Almahdi M, Bauer R, Beach T, Chen K. Banner Alzheimer's Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Rapidly progressive Alzheimer's disease (rpAD) is putative subtype of AD characterized by rapidly progressive cognitive decline and/or short disease duration. Although a consensus definition of rpAD has not been established, these patients have been variously defined in terms of a MMSE score point decrease of >3 points/6 months or >5 points/year. Depending on the definition, it estimated that 10% to 30% of AD cases are rpAD. At present, little is known about the clinical manifestations, genetic factors, CSF and/or plasma biomarker characteristics, or post-mortem features associated with rpAD. Better characterization and understanding of rpAD could contribute to both clinical practice and clinical trial design.

Methods: Using data from the Banner Sun Health Research Institute Brain Body Donation Program (BBDP), we explored various operational definitions of rpAD to better understand the patterns of short-term rapid decline in the context of the entire disease course. rpAD and matched control patients were compared using pathology categories for AD-specific lesions, comorbid neurodegenerative conditions and comorbid cerebrovascular conditions. We then explored the overall relationship of the annualized rate of MMSE decline with each of the variables using the non-parametric rank-order association based on Kendal tau-b test and not correcting for multiple comparisons. Secondly, we investigated the variation of each demographic, clinical, and neuropathological measure among the five groups with different decline rates (as detailed below). All statistical analyses were carried out using Statistical toolbox and our own codes in MATLAB.

Results: We identified 731 subjects in the BBDP who had received a diagnosis of dementia during life and had evidence of NIA-Reagan intermediate or high neuropathologic changes at autopsy. 600 of these subjects had a least 2 visits with acquired MMSEs and were included in the initial analysis. We calculated the annual rate of MMSE change for this group, and 271 had an annualized increase of ≥ 3 points/year and 229 had a rate of < 3 points/year. In order to improve the robustness of the MMSE data, we performed additional filtering to only include subjects whose two adjacent MMSE visits were at least 3 months apart and the initial MMSE score was > 20 . In addition, we excluded subjects whose last MMSE assessments were more than 2 years before death. This yielded a total of 585 subjects with a mean annualized rate of decline of -2.5 points/year (SD 2.3). We further divided this group into 5 categories, annualized decline of < 1 point/year (n=10), between 1 and -2 points/year (n=265), < -2 to -5 points/year (n=225), < -5 to -10 points/year (n=79), and < -10 points/year (n=6).

With the exception of Lewy Body score which was positively correlated to the rate of decline (Chi-square test, $p=0.016$), we did not identify any demographic, clinical or neuropathologic variable that was correlated with the annualized rate of decline on MMSE. To account for possible differences in the rates of "pathologic load" development, we then divided neuropathologic variables such as Braak score, plaque count or neurofibrillary tangle total, by years of illness, but this also did not need yield any significant correlations.

Conclusions: The results confirm a faster decline rate in AD with comorbid Lewy body disease. Although other key drivers were not identified, examination of the results revealed some consistent trending contributions from multiple demographic, clinical and neuropathological measures.

IDENTIFICATION OF TRANSCRIPTIONAL PATTERNS IN HIPPOCAMPUS CA1 SUBREGION ASSOCIATED WITH DIFFERENTIAL COGNITIVE APTITUDE ACROSS THE ENTIRE LIFESPAN OF RATS. Chawla M, Chen YJ, Zempare M, Barnes CA, Dalmendray A, Young K. University of Arizona; Arizona Alzheimer's Consortium.

Background: Each hippocampus primary cell type has a unique transcriptomic composition. Therefore, it is possible that CA1 and CA3 pyramidal cells or DG granule cells may have distinct age-sensitive trajectories. Additionally, these trajectories of cognitive decline may depend on the cognitive status of individual rats.

Methods: Here we utilize the immediate early gene Arc to assess the transcription pattern in cognitively categorized rats. Male Fisher-344 rats (6 mo, 15 mo, and 23 mo old), were given a battery of cognitive tests and were categorized into three groups - low, average, or high performers depending on their performance on the spatial version of the Morris watermaze. Rats were given two-5 min exploratory sessions separated by a 20 min rest in the home cage and brains from behavior as well as two additional controls (caged, a negative control, and maximal electroconvulsive shock-treated, a positive control) were quickly extracted, hemisected and rapidly frozen until sectioning and processing for in situ hybridization. In situ hybridization was performed as described previously (Guzowski et al., 1999), and slides were imaged using an SP5 Leica or a Zeiss LSM 880 confocal microscope. Three different areas of CA1 were imaged: distal CA1, which receives input primarily from the lateral entorhinal cortex; proximal CA1, which receives inputs primarily from the medial entorhinal cortex; and middle CA1, which receives a mixture of entorhinal inputs. Cells with Arc mRNA expression in the nucleus, cytoplasm or both compartments were counted using Image J software.

Results: Since cell-counting is still ongoing, we can report that Arc mRNA expression is following a pattern similar to that of previous studies; that is, very low Arc expression in caged controls, robust expression in maximal electroconvulsive shock-treated rats and intermediate in behavior-treated rats.

Conclusions: Using compartment analysis of temporal activity using FISH (catFISH) we can determine the reliability of cell firing in brain networks by two experiences in the same environment separated by 20 minutes. In this manner, we can assess the circuit stability of these specific brain regions, across age and across different cognitive competences. The overall goal is to identify the circuit characteristics associated with successful cognitive outcomes during normal aging.

PREDICTING THE PACE OF MCI PROGRESSION TO AD BASED ON MULTI-MODALITY NEUROIMAGING DATA BY A NOVEL HYBRID ORDINAL LEARNING ALGORITHM. Wang L, Su Y, Zheng Z, Chen K, Weidman D, Wu T, Lo S-C, Lure F, Li J. Georgia Institute of Technology; Banner Alzheimer's Institute; Arizona State University; MS Technologies Corp; Arizona Alzheimer's Consortium.

Background: Machine learning (ML) has shown great promise for integrating multi-modality neuroimaging datasets to predict the risk of converting to AD for individuals with Mild Cognitive Impairment (MCI). Most existing work aims to classify MCI patients into converters versus non-converters. The limitation is a lack of granularity in differentiating MCI patients who convert at different paces. Pace prediction has important clinical values by allowing for more personalized interventional strategies, better preparing patients and their caregivers, and facilitating patient selection in clinical trials. We proposed a novel Hybrid Ordinal Learning (HOL) algorithm for pace prediction of MCI conversion to AD.

Methods: This study focused on the amyloid-positive MCI patient cohort in ADNI for the pace prediction, which included 282 samples. The datasets included baseline T1-MRI, amyloid-PET, MMSE, CDR, age, gender, years of education, and APOE status. ROI-based structural measures were computed from T1-MRI using FreeSurfer v7.1 and regional SUVR measures were computed using our in-house pipeline from amyloid-PET. HOL was trained to predict the conversion to AD for each MCI patient into four ordinal classes representing four fast-to-slow paces of conversion, e.g., conversion in the first year, not in the first but in the second year, not in the first two years but by the fifth year, and not in the first five years, respectively. The novelty of HOL compared to existing ordinal classification algorithms was its capability of leveraging imperfectly-labeled samples in the training set to build a robust learner.

Results: Under cross-validation, HOL achieved 0.83 in accuracy, balanced across the different paces, based on a combination of 314 features from MRI, PET, and clinical data, while the conventional ordinal SVM classifier achieved only 0.68 in accuracy.

Conclusions: We demonstrated that a novel ML algorithm, HOC, could achieve high accuracy in predicting the pace of conversion to AD for MCI patients. Future research is needed to validate the research finding with larger datasets.

PREDICTION OF THE ALZHEIMER'S DISEASE RISK USING TAU-PET AND MACHINE LEARNING. Wang L, Su Y, Zheng Z, Chen K, Weidman D, Wu T, Lo S-C, Lure F, Li J. Georgia Institute of Technology; Banner Alzheimer's Institute; Arizona State University; MS Technologies Corp; Arizona Alzheimer's Consortium.

Background: Alzheimer's Disease (AD) is a devastating neurodegenerative disease characterized neuropathologically by amyloid plaques and tau tangles. Recent advances in positron emission tomography (PET) imaging allows quantitative and in vivo mapping of tau pathology across the brain. In this work, we develop machine learning (ML) algorithms to leverage this new imaging modality to derive useful information and facilitate diagnostic/prognostic decision making.

Methods: We used data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) databases including 67 AD, 393 NC, and 144 MCI subjects with tau-PET images. Among the MCI patients, 31 converted to AD within 24 months (converters), while 113 did not (nonconverters). Tau-PET images were processed by the ADNI PET core to generate regional standardized uptake value ratios (SUVRs) with inferior cerebellum referencing, among which 84 cortical and sub-cortical SUVR features were included in ML training. In addition to imaging features, demographic and cognitive features such as sex, age, MMSE scores were also included. Four ML classifiers including Random Forest (RF), Gaussian Process (GP), Support Vector Machine (SVM), and logistic-lasso were first trained for the NC vs. AD classification task with 10-fold cross-validation. In addition to providing a binary classification based on each scan, the trained classifiers also provide AD risk scores which are applied to scans from the MCI patients to predict the probability of conversion to AD in 24 months.

Results: The four models achieved on average 0.89 accuracy, 0.80 sensitivity, and 0.91 specificity in classifying NC vs. AD. The classification results by the different ML models had an average ICC of 0.83 indicating a high level of agreement. Model performance improved to 0.95 accuracy, 0.91 sensitivity, and 0.95 specificity, when sex, age, and MMSE were included in the models. When the ML models were applied to the MCI patients and using a probability cutoff of 0.5, the trained classifiers achieved on average 0.77 accuracy, 0.82 sensitivity, and 0.75 specificity in predicting MCI conversion. Furthermore, the rank correlation between the predicted probabilities and the conversion times of all MCI patients was -0.69. The agreement of the classification results on each MCI subject by the different algorithms is high with an average ICC of 0.85. When non-imaging features were included the average model performance was 0.79 accuracy, 0.78 sensitivity, and 0.79 specificity, which did not significantly improve.

Conclusions: The trained ML classifiers based on tau-PET data achieved high accuracy in differentiating NC and AD patients as well as predicting the risk of conversion to AD for MCI subjects. Further investigation is ongoing to understand the contribution of different features to the predictive model.

SELF-SUPERVISED CONTRASTIVE LEARNING TO PREDICT ALZHEIMER'S DISEASE PROGRESSION WITH 3D AMYLOID-PET. Kwak M-G, Su Y, Chen K, Weidman D, Wu T, Lo S-C, Lure F, Li J. Georgia Institute of Technology; Banner Alzheimer's Institute; Arizona State University; MS Technologies Corp; Arizona Alzheimer's Consortium.

Background: Early diagnosis of Alzheimer's disease (AD) is an important task that facilitates the development of treatment and prevention strategies and may potentially improve patient outcomes. Neuroimaging has shown great promise, including the amyloid-PET which measures the accumulation of amyloid plaques in the brain – a hallmark of AD. It is desirable to train end-to-end deep learning models to predict the progression of AD for individuals at early stages based on 3D amyloid-PET. However, commonly used models are trained in a fully supervised learning manner and they are inevitably biased toward the given label information. To this end, we propose a self-supervised contrastive learning method that can leverage unlabeled data and evaluate this method using the task of predicting AD progression based on 3D amyloid-PET.

Methods: Amyloid PET data in 612 MCI participants at baseline from ADNI was included in this study. The individuals who converted to AD within 36 months were assigned as converters, and the individuals who did not convert were assigned as non-converters. There were 158 converters and 463 non-converters, and additionally 443 unlabeled MCI images due to a lack of follow-up data at or after 36 months. The imaging data were processed in-house and spatially normalized to the MNI template space. The overall model can be divided into a self-supervised learning step where the semantic data representations are learned through instance discrimination without any label information, i.e. converters/non-converters, and a supervised learning step where only labeled data were used to optimize the final classifier. A 3D ResNet-50 model architecture was adopted with an output dimension of 128, a two-layer perceptron was used as the fully connected layers. The labeled data was split 90/10% for 10-fold cross-validation, and the full unlabeled dataset was used for the first step.

Results: A fully supervised model trained using labeled data only achieved an AUROC of 0.8166, with 77.77% accuracy, 73.24% sensitivity, and 79.01% specificity. Our proposed approach leveraging both labeled and unlabeled data achieved an AUROC of 0.8528, with 81.19% accuracy, 77.43% sensitivity, and 82.28% specificity.

Conclusions: In this work, we proposed a self-supervised contrastive learning method to leverage both labeled and unlabeled data. We applied this method to the MCI converter vs. non-converter classification task based on amyloid PET data. The proposed method achieved improved model performance. Further investigation is ongoing to extend our work by including non-imaging data and additional imaging modalities.

VIRTUAL ENVIRONMENT GROCERY STORE FOR ASSESSING AGING COGNITION.
Parsons TD. Arizona State University; Arizona Alzheimer's Consortium.

Background: Although neuropsychologists are increasingly asked to assess an individual's everyday memory abilities, research suggests that people expected to perform poorly on neuropsychological tests may perform within normal limits. Virtual reality (VR) is a relatively new technology that aims to develop and implement ecologically valid and interactive 3D simulations of real-world scenarios. VR assessments offer potential to address the ecological validity limitations found in traditional measures.

Methods: The Virtual Environment Grocery Store (VEGS) is a virtual multiple errands platform with various shopping tasks. The VEGS assesses episodic and prospective memory. Validation of the VEGS is needed. Several validation studies are underway with both clinical and nonclinical populations. Participants include community dwelling healthy adults, persons with dementia, and college age students. To investigate the construct validity of a newly developed virtual reality measure of memory (i.e., the VEGS), traditional neuropsychological measures of memory and executive functioning were administered.

Results: Performances on the VEGS memory tasks (in the low distractor condition) and the traditional neuropsychological assessments of memory were positively correlated, indicating that memory for VEGS content was similar to memory for traditional paper-and-pencil measures. Significant differences were found between groups for the VEGS memory and multitasking measures. Performances on the VEGS memory tasks in the high distraction condition also revealed correlations with the traditional neuropsychological assessments of memory. The addition of distractors into the virtual environment resulted in significant correlations with traditional measures of inhibitory control.

Conclusions: The VEGS has the advantage over traditional measures of providing objective measurement of individual components of memory in simulations of everyday activities.



Institutional Information

Research Summaries and Key Personnel From Each Participating Institution

ARIZONA STATE UNIVERSITY

Over a decade ago, Arizona State University (ASU) set forth to redefine 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, focusing attention 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 seven years (2015-2021). 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 exemplifies the type of endeavor that ASU seeks to promote, and a focus on innovative approaches is most certainly critical to research and treatment efforts.

For the Arizona Alzheimer's Consortium, ASU provides the Outreach and Recruitment Core (Dr. David W. Coon) and Research Education Component (Dr. Heather Bimonte-Nelson). These serve researchers throughout the state as part of the Consortium's NIA-sponsored Arizona Alzheimer's Disease Center. The ASU team includes leaders in the development of novel models to advance our understanding of the mechanisms that potentially modulate the short- and long-term neurological consequences of SARS-CoV-2 infection (Brafman laboratory); identification and testing of promising anti-tau therapeutics to treat AD (Sierks laboratory); explore injury-induced neuroinflammation as a contributor to Alzheimer's Disease (Stabenfeldt laboratory); characterize the microbiome of post-mortem brain tissue in subjects affected by Alzheimer's disease (Readhead laboratory); explore possible links between gut tissue microbiota and APP processing (Mastroeni laboratory); compare age-related responses to menopause variations on brain function by testing whether hysterectomy at younger versus older age impacts brain functioning differently (Bimonte-Nelson and Wilson laboratories); build and deliver novel and efficient imaging algorithms that utilize sMRI to predict A β and tau burden with excellent biological interpretability (Wang laboratory); develop mobile phone version of online motor-cognitive game to increase underrepresented minority participation (Schaefer laboratory); examine aging effects and sex differences in depression and poor cognition associated with steroid treatment (Conrad laboratory); and, develop and test multicomponent interventions for individuals with MCI or ADRD and their family caregivers (Coon laboratory). It is noteworthy that ASU has numerous scientific research domains that are being further developed and strengthened to bolster the impact on Alzheimer's disease and aging research, with a focus on discovery and action to move trajectories, diagnosis, and treatment 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 Alzheimer's disease, as well as to optimize the trajectory of brain aging, using both preclinical and clinical approaches. 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 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 ASU-Banner Neurodegenerative Disease Research Center (NDRC)¹ led by Dr. Jeffrey Kordower. 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. Located within the Biodesign

Institute at ASU, the Center is expected to accommodate nearly 20 laboratories led by research scientists from a variety of fields, including computer science, biology, engineering, chemistry and more. The Center fosters push-pull relationships between big data and other analyses of post-mortem and other human data sets and experimental models and leverages an emerging collaboration among 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.

In 2021, ASU opened the ASU Health Futures Center, a collaboration between ASU and the Mayo Clinic with the shared goal of improving health and well-being outcomes in the community. The center offers the community a chance to participate in a world-class research, innovation and learning environment. The leading-edge facility will feature a med-tech innovation accelerator, biomedical engineering and informatics research labs, and an innovative education zone. Programs from several ASU schools and colleges will benefit from the proximity of this facility to the Mayo Clinic Hospital and Cancer Center. ASU programs include Edson College of Nursing and Health Innovation, the College of Health Solutions, Fulton Schools of Engineering, and Entrepreneurship and Innovation, as well as collaborative programs within the Mayo Clinic.

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, to postdoctoral fellows. The approach to training is hands-on, multifaceted, and interdisciplinary, with the goal to engage 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) and reflects this strong and extensive training commitment. Notably, ASU offers graduate degrees in Statistics and Biomedical Informatics, the Behavioral Neuroscience Program² within the Department of Psychology, as well as the Interdisciplinary Graduate Program in Neuroscience³. The latter two training programs focus upon approaches that integrate multiple levels of analysis using systems and interdisciplinary approaches – cellular, behavioral, and cognitive – to address preclinical, clinical, and translational questions about brain and behavior relationships.

¹ <https://science.asu.edu/neurodegenerative-disease-research-center>

² <https://psychology.clas.asu.edu/content/psychology-behavioral-neuroscience-phd>

³ <https://neuroscience.asu.edu>

ARIZONA STATE UNIVERSITY

Name	Degree	Role
Bimonte-Nelson, Heather	PhD	President's Professor
Bjorklund, Reed	PhD	Postdoctoral Fellow
Braden, Blair B.	PhD	Assistant Professor
Brafman, David	PhD	Associate Professor
Carbajal, Berta	--	Research Specialist/Outreach and Recruitment
Carll, Phil	MSW	Research Specialist/Interventionist
Carlye Frisch	BS	Graduate Researcher
Coleman, Paul	PhD	Research Professor
Conrad, Cheryl D.	PhD	Professor
Coon, David W.	PhD	Director, Center for Innovation in Healthy and Resilient Aging; Professor
Cordova, Lourdes	--	Research Specialist/Outreach and Recruitment
Covarrubias, Aidee	--	Research Specialist/Outreach and Recruitment
Dunckley, Travis		Assistant Research Professor
Essuman, Albert	MS	Research Technician
Galyon, Brooke	BS	Research Technician
Gayathri Srinivasan	MS	Graduate Researcher
Glinka, Allison	MS	Project Coordinator
Han, SeungYong	PhD	Assistant Research Professor
Huseby, Carol	PhD	Assistant Research Professor
Judd, Jessica		Postdoctoral Research Scholar
Kordower, Jeffrey H.	PhD	Professor & Director, ASU-Banner Neurodegenerative Disease Research Center
LaBaer, Joshua	MD, PhD	Professor & Executive Director, Biodesign Institute
Lauren Baker	BS	Graduate Researcher
Li, Baoxin	PhD	Professor
Maxfield, Molly	PhD	Associate Professor
Mastroeni, Diego	PhD	Assistant Research Professor
Maxfield, Molly	PhD	Associate Professor
Morales, Abigail G.		Graduate Research Assistant
Panayi, Nicholas	PhD	Grad Research Associate
Perdoza, Morgan	BS	Research Technician
Perez, Sydney	BS	Research Specialist/Interviewer

ARIZONA STATE UNIVERSITY

Name	Degree	Role
Pesheva, Anna	--	Undergraduate Researcher
Readhead, Benjamin	MBBS	Assistant Research Professor
Schaefer, Sydney	PhD	Assistant Professor
Sierks, Michael	PhD	Professor
Shah, Jay	MS	Graduate Researcher
Stabenfeldt, Sarah	PhD	Associate Professor
Tu, Yanshuai	MS	Graduate Researcher
Velazquez, Ramon	PhD	Assistant Professor
Wang, Qi	PhD	Assistant Research Professor
Wang, Yalin	PhD	Associate Professor
William Kostes	BS	Graduate Researcher
Wilson, Melissa	PhD	Associate Professor
Wu, Jianfeng	BS	Graduate Researcher
Wu, Teresa	PhD	Professor
Yu, Fang	PhD, RN	Professor
Zhu, Wenhui	BS	Graduate Researcher

BANNER ALZHEIMER'S INSTITUTE

The Banner Alzheimer's Institute (BAI) has three goals: To find treatments to prevent Alzheimer's disease (AD) without losing a generation, to set a new standard of care for patients and families, and to promote a model of multi-institutional collaboration in biomedical research. BAI is intended to accelerate the evaluation, approval and availability of treatments to postpone, reduce or completely prevent the clinical onset of AD as quickly as possible; leverage its brain imaging resources and expertise to advance the scientific study, early detection, tracking, diagnosis, treatment and prevention of AD and related disorders; address the medical and nonmedical needs of affected persons and families to the fullest extent possible, and help to establish a new standard of dementia care in the emerging population-based healthcare financing system. Finally, it is intended to complement, enhance, and benefit from close working relationships with its organizational partners inside and outside of the Arizona Alzheimer's Consortium (AAC).

BAI's Stead Family Memory Center 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 illness. It provides educational, outreach and research enrollment programs for Arizona's Native American and Latino communities, evaluates and follows Native Americans in the NIA-sponsored Arizona AD Research Center's (ADRC) Clinical Core, and oversees an Annual Conference on AD and Dementia in Native Americans. Its Banner Dementia Care Partners is seeking to demonstrate ways in which to optimize the identification and evaluation of cognitive problems, address a broad range of the affected person's and family's medical and non-medical needs, reduce unnecessary hospitalizations, and is affordable to payers in the emerging healthcare financing system. BAI conducts numerous clinical trials of investigational treatments, including those in the Alzheimer's Prevention Initiative (API). Its researchers also help oversee prospective 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.

Its state-of-the-art NIH-supported 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. In collaboration with Mayo Clinic, it includes a 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. In collaborations with the University of Antioquia and Massachusetts General Hospital, it also includes a study of PSEN1 E280A mutation carriers and non-carriers from the world's largest autosomal dominant AD kindred in Colombia. It has been a member of the AD Neuroimaging Initiative (ADNI) PET Core, where it is responsible for the development, testing and use of voxel-based image analysis techniques with improved power to detect and track AD. It has played pioneering roles in the study of preclinical AD. 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. AARC funds complement research activities supported by competitive grant awards from several NIA-sponsored research grants,

private foundation grants, and clinical trials. In conjunction with our NIA-sponsored ADRC, subjects, images, other data, and image-analysis techniques from our study of cognitively normal APOE ϵ 4 carriers and non-carriers provide a core resource for interested investigators inside and outside of Arizona.

In the next few years, BAI, BSHRI, and their partners will place a growing emphasis on the acquisition of antemortem brain-imaging, CSF, and blood-based biomarkers for AD and related disorders in their longitudinal cohorts and help to find and support the use of promising amyloid and other blood tests for AD and related disorders. These organizations, TGen, and ASU (e.g., at the ASU-Banner Neurodegenerative Disease Research Center [NDRC]) are also developing 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 are using big data analytical techniques to characterize networks and drivers at which to target in the discovery of new treatments. They and their organizational partners will also be exploring targets at which to aim APOE modifying treatments. BAI has created a new clinical and research facility to advance the fight against AD, Dementia with Lewy Bodies and related diseases in Tucson in collaboration with the University of Arizona, providing ways in which to further address the medical and non-medical needs of patients and family caregivers, provide clinical and biomarker evaluations for collaborative research studies of AD and brain aging, and evaluate investigational treatment and prevention therapies in clinical trials.

With several hundred million dollars in NIH, philanthropic and industry support, API has helped to launch a new era in AD prevention research, lead studies on the science of participant recruitment and engagement with the goal of increasing diversity among individuals in registries and AD trials, develop platforms to disclosing genetic and biomarker AD-risk results to individuals and understand the impact of learning those results, accelerate the evaluation of prevention therapies, and help to find and support the approval, availability and affordability of prevention therapies as soon as possible. It includes a growing number of preclinical AD / theragnostic biomarker development trials in persons who, based on their genetic or biomarker findings, are at increased AD risk, including the recently completed Banner, Roche and NIA supported API ADAD Colombia Study in the world's largest autosomal dominant AD (ADAD) kindred, the recently discontinued Banner, Novartis, Amgen and NIA-supported, international API Generation Studies 1 and 2 in persons at particularly high risk for the clinical onset of late-onset AD, the Roche-supported and API-co-led (in collaboration with the A4 leaders from USC and MGH) Skyline study of an amyloid- β plaque-reducing antibody therapy in cognitively unimpaired amyloid- β positive adults that includes 2 NIA-supported ancillary studies; the Lilly-supported and API-co-led Trailblazer ALZ-3 study of another amyloid- β plaque-reducing antibody therapy in cognitively unimpaired persons with blood-based biomarker evidence of amyloid- β plaque burden; and other prevention and early-phase AD-modifying drug and gene therapy and blood pressure-lowering drug trials TBD. These and other trials are intended to evaluate the investigational treatments in potentially license-enabling prevention trials; to provide a better test of the amyloid hypothesis than trials in the later preclinical or clinical stages of AD; establish the extent to which a treatment's different biomarker effects are associated with a clinical benefit and provide evidence to support their use as reasonably likely surrogate endpoints in future 24-month prevention trials; provide a shared resource of data and biological fluids for the research community after the trial is over; complement, support and providing a foundation for other prevention trials; to help clarify the benefits, risks and role of APOE genetic and amyloid test results disclosure in the era of Alzheimer's prevention trials; support the advancement of Alzheimer's prevention research in the Collaboration for Alzheimer's Prevention CAP); empower persons at highest risk in the scientific fight against AD; and provide a fighting chance to find and support approval of an AD prevention therapy by 2025, a primary goal of the National Plan to Address AD.

API also includes exceptionally large registries to support interest and possible enrollment in prevention studies. In partnership with the University of Antioquia, the API Colombian Registry, in collaboration now includes ~6,000 members of the PSEN1 E280A mutation kindred, including nearly 1,200 mutation carriers, who have provided their DNA and had clinical and neuropsychological evaluations. The Banner-led, web-based Alzheimer's Prevention Registry (www.endALZnow.org) provides information about advances in prevention research and opportunities to enroll in prevention trials to >380000 people and continues to grow rapidly; our GeneMatch Program (www.endALZnow.org/genematch) has enrolled >100,000 persons ages 50-90 and continues to add new members daily. Both Banner-led programs connect interested participants to studies taking place in their communities and continue to advance efforts to identify and support enrollment in prevention trials (e.g., using an amyloid- β blood tests), and to address the logistical, ethical, and scientific issues involved in this endeavor.

The API ADAD Colombia Trial was recently completed. While the anti-oligomeric amyloid- β antibody therapy crenezumab failed to demonstrate a statistical significant benefit, this first-of-its kind study demonstrated the ability to conduct a potentially license-enabling AD prevention trial in cognitively unimpaired persons at genetic risk, introduced ways to accelerate the evaluation and approval of prevention trials, addressed scientific, social, ethical and risk disclosure challenges, demonstrated the ability to conduct a trial of an experimental drug therapy in a vulnerable population from a developing country that was highly valued by the research participants themselves. It led to a growing number of prevention trials led by API, industry partners and other organizations, and has given the field a fighting chance to find and support the approval of an effective prevention therapy within the next few years. The trial will provide an invaluable resource of cognitive, clinical, brain imaging, CSF and blood-based biomarker data and CSF, blood and DNA samples to the scientific community to inform the design of future prevention trials and support the study of preclinical AD.

Other API-related prevention trials have the potential to find and support approval of a prevention therapy within the next few years. For instance, Trailblazer ALZ-3 trial has introduced a strategy to enroll a remarkably large number of cognitively unimpaired persons with plasma p-tau217 evidence of amyloid- β plaque burden, including those from under-represented ethnic, racial and geographic groups, a decentralized trial design that allows persons to be assessed virtually in their own homes. The Skyline trial will permit the evaluation of another promising antibody therapy and, with NIA grant support, help to evaluate more efficient ways to disclose a person's biological and genetic risk, and provide a shared resource of data and samples to support the evaluation of promising blood-based biomarkers.

BAI has several specific aims:

1. To leverage our 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 our imaging resources in the early detection and tracking of related diseases (e.g., chronic traumatic encephalopathy [CTE]).
3. To implement, test 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 participant recruitment registries.
6. To introduce a new 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 support the evaluation of non-medication prevention therapies that are intended to promote cognitive health.
8. To advance the science of research participant engagement and AD study participation, including in underrepresented groups.
9. 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 find 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.
10. To provide a care model that more fully address the needs of patients and families and BAI, and to develop and test 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 Partners.
11. To support the clinical research and Native American outreach, education and enrollment goals of the Arizona ADRC.
12. 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

Name	Degree	Role
Alexander, Robert	MD	Sr. Director, Chief Scientific Officer, API
Amador, Ricardo R.	MS	Clinical Research Program Manager
Anderson, Allan	MD	Director, BAI Tucson
Anguiano, Jaynie	--	Clinical Research, BAI Tucson
Ashish, Dev	PsyD	Neuropsychologist, BAI Tucson
Autry, Lynn	BS, BA	Psychometrist
Bandy, Dan	MS, CNMT	PET Technical Director and Sr. Scientist
Battraw, Angelena	--	Clinical Research Assistant
Bauer III, Robert	BS	IT Systems Analyst
Boker, Connie	MBA	Director, BAI Imaging Center
Brand, Helle	PA	Physician Assistant
Cardenas, Melissa M.	FNP	Nurse Practitioner, Neurology
Chen, Kewei	PhD	Sr. Scientist, Co-Leader ADRC Data Management and Statistics Program
Chen, Yinghua	MS	Bioinformatics Analyst
Copeland, Jacquelynn	PhD	Neuropsychologist
Craig-Muller, Jennifer	BS	Clinical Research Program Senior Manager Director, All of Us Research Program
DeMarco, Kathryn	BS	Clinical Research Program Manager
Devadas, Vivek	BS	Information Analyst
DiLise-Russo, Marjorie	--	Sr. Psychometrist
Edmonds, Emily	PsyD	Neuropsychologist
Ghisays, Valentina	PhD	Bioinformatics Scientist
Gonzalez-Green, Ricquee	--	Clinical Research Representative
Gopalakrishna, Ganesh	MD	Associate Director, Stead Family Memory Center
Goradia, Dhruvan	PhD	Bioinformatics Scientist
Guebara, Ruben L.	--	Jr. Radiochemist
High, Nellie	M.Ed	Clinical Research Program Mgr, API
Jaeger, Chad	BS	COO, Banner Research
Jakimovich, Laura	RN	Multi-Center Clinical Trials Manager
James, Michelle	PsyD	Neuropsychologist
Joshi, Pallavi	MD	Physician
Kavathas, Spiro	BA	Radiochemist

BANNER ALZHEIMER'S INSTITUTE

Name	Degree	Role
Koren, Andrei	PhD	Senior Scientist, Lab Head Radiochemistry
LaBenz, Greg	--	Clinical Research Assistant
Langbaum, Jessica	PhD	Director, Alzheimer's Prevention Initiative (API)
Lee, Wendy	MS	Senior Manager, Research Bioinformatics
Lindemer, Shannon	--	Psychometrist, BAI-Tucson
Lomay, Nicole	BS	Native American Outreach Representative
Luo, Ji	MS	Bioinformatics Analyst
Madrid, Mayra	--	Clinical Research Coordinator
Malek-Ahmadi, Michael	PhD	Bioinformatics Scientist
Malone, Matthew	MD	Physician, BAI-Tucson
Mulder, Heather	BS	Associate Director of Outreach Services
Nisson, Lori	MSW,LCSW	Director, Family & Community Services
Ochoa, Cassandra	RDN	Clinical Research Program Mgr, API
Paco, Alice N.	--	Psychometrist, BAI-Tucson
Paone, Joshua	--	Clinical Research Coordinator
Parkhurst, David	--	Clinical Research Program Manager
Pazzi, Marjorie M	BS	Director, Clinical Trials, BAI Tucson
Perrin, Allison	MD	Physician Dementia Specialist
Protas, Hillary	PhD	Bioinformatics Scientist
Pruzin, Jeremy	MD	Physician
Rainey, Joseph C	--	Clinical Research Representative, BAI-Tucson
Rapcsak, Steven	MD	Associate Director, Clinical Trials, BAI-Tucson
Reiman, Eric	MD	Executive Director, BAI Director, Arizona Alzheimer's Consortium and NIA-supported Arizona ADRC
Richter, Nicole K	BS	Radiochemist
Rico, Kristina M	--	Clinical Research Coordinator, BAI-Tucson
Robinson, Jaclyn M	MD	Physician, BAI-Tucson
Saner, Don	MS	Senior Director, Data Science; Co-Leader, ADRC Data Management and Statistics Program
Simmonds, Isaac	--	Radiochemist
Sipes, Joshua	--	Clinical Research Program Manager, BAI-Tucson
Sohankar, Javad M	PhD	Data Scientist

BANNER ALZHEIMER'S INSTITUTE

Name	Degree	Role
Su, Yi	PhD	Director, Computational Brain Imaging Analysis Program; Co-Leader, ADRC Data Management and Statistics Program
Taha, Basel	--	Clinical Research Representative
Tariot, Pierre	MD	Director, BAI
Tsai, Po-Heng	MD	Physician Dementia Specialist, Memory Center
Vadovicky, Sheila	--	Psychometrist
Weidman, David	MD	Associate Director, BAI Clinical Trials

BANNER SUN HEALTH RESEARCH INSTITUTE

Banner Sun Health Research Institute (BSHRI) was established in 1986 in the heart of Sun City, Arizona, the nation's first planned retirement community, including more than 100,000 older adult residents in the area, and intended to make a profound difference in the scientific study of Alzheimer's disease (AD) and Related Dementias (ADRD), Parkinson's disease (PD), other age-related brain disorders, and healthy aging.

BSHRI includes: **a)** A world-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, Family and Community Services, and the Neuro Wellness Program; **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 psychosocial factors associated with successful cognitive aging that includes 1,552 research participants enrolled all-time (544 active: of these 67% of participants female, 328 are ≥ 80 years of age, 218 are ≥ 85 , 100 are between 90-99, and 2 are 100 years or older. 56% of active subjects ≥ 85 , the oldest old, a rapidly growing demographic in AZ and the U.S. in whom there is a paucity of data regarding cognitive aging); as well as a free, community service, Brain Health Check-In (BHCI) Program (706 BCHIs performed since established in 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 >120 education programs per year (nationally, internationally, regionally and locally – including in-person, hybrid, virtual, webcasts and podcasts) and leadership in world-renowned continuing education programs; training in neurology, neuropsychology and neuropathology for students and post-doctoral fellows; neurology residents; a highly productive summer research internship program for under-represented and other college and high school 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; **g)** annually >80 publications, and >70 scientific/medical presentations at conferences and meetings; and **h)** Where historically, the state's largest number of productive basic scientists in the fight against AD, renowned for major contributions to study of amyloid and tau processing, brain inflammation, epigenetics, and the roles of cholesterol and cerebrovascular disease in AD, were located; these basic science programs completed relocation to ASU. Previously, BSHRI served as the applicant organization for the Arizona ADCC on behalf of the organizations in the AAC, and it remains home to the NIA-funded AZ ADRC's Administrative Director, Andrea Schmitt; Neuropathology Core Director, Dr. Thomas Beach; and Clinical and Biomarker Cores Co-Leader, Dr. Alireza Atri.

The world renowned BBDP, directed by Thomas Beach, MD, PhD, includes ~ 700 actively followed, clinically characterized and longitudinally assessed participants, including patients with AD, PD, and related disorders, and older adults with cancer or who are cognitively and neurologically unimpaired at the time of their enrollment. Participants consent to undergo detailed annual assessments (many include blood and neuroimaging) during life and then donate their brains and/or bodies after death. The BBDP is unique for: **a)** its rapid autopsy program, with a

median 3-hour post-mortem interval allowing unusually high tissue quality, optimizing post-mortem discovery research on >2,500 expired donors, who have had comprehensive neurological and cognitive assessments during life and neuropathological examinations after death; **b)** a large number of brain donors who are cognitively and neurologically unimpaired at the time of their clinical enrollment, thereby advancing the study of preclinical AD and PD and providing clinically and neuropathologically normal control subjects for genetic and other research studies; **c)** whole body donation, banked organs and tissues from >800 expired donors since 2005, and the opportunity to relate brain pathology to biological features of other body organs; and **d)** ~275 annual tissue distributions to advance research in Arizona and globally. The BBPD includes hundreds of participants in the AZ ADRC's Clinical and Ancillary BBPD Cores and the ADCC's Neuropathology Core (in partnership with Mayo Clinic Arizona, Barrow Neurological Institute and Banner Alzheimer's Institutes in Phoenix and Tucson). The BBPD plays critical roles in the neuropathological validation of amyloid/tau PET, and other emerging ante-mortem biomarkers, such as fluid biomarkers, during and at the end-of-life (e.g., hospice), thus contributing to the validation of blood-based biomarkers and FDA approvals of molecular imaging/PET ligands. The BBPD provides a tissue resource for genome-wide genetic, transcriptomic and proteomic data from different brain regions and cell types, and annually contributes to >100 research studies, collaborations, and grants, >60 annual journal publications, and highly impactful findings and invited lectures and presentations at prestigious scientific/medical conferences.

BSHRI has undergone significant progress and changes since 2016, shifting focus from basic sciences to clinical and translational science and clinical services; 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 (BSHRI & BAI) AD/ADRD-related clinical, family and community services and research programs including the Dementia Care Partners community care navigation and support; and diversity, equity and inclusion partnerships and programs; **b)** Growth of comprehensive multidisciplinary services at The Cleo Roberts Memory and Movement Disorders Centers including recruitment of multiple clinicians/clinician-scientists; **c)** Implementation and expansion (AAC pilot funding to PI Dr. Danielle Goldfarb, Dr. Alireza Atri, Co-I) of an ultrasound lumbar puncture (LP) program which was recently awarded developmental project funding by the ADRC; **d)** Launch and expansion of the Brain Health Check-In (BHCI) community service program at the Center for Health Aging; since 12/2018 walk-in or scheduled BHCI have provided >700 individuals with free brain health concern status assessments along with feedback, information, education, resources and referrals; **e)** Enhancing clinical and biological (biofluid/serum) characterization of the BSHRI's Longevity Study cohort (see AAC funding report, Dr. Alireza Atri PI), harmonizing important elements, and increasing co-enrollment in the Longevity Study and BBPD programs; **f)** Ongoing strategic planning for the development and further growth of clinical, aging and clinical/translational 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 >150 international, national, regional, and community presentations per year; BSHRI staff provided >14,500 person/hours of medical/health professional education, scientific or community lectures, presentations and programs, including co-sponsoring and co-directing (Dr. Atri) the world-renowned Harvard Medical School annual 4-day CE course (Dementia: A Comprehensive Update), and the annual BSHRI Alzheimer's, Lewy Body and Related Dementia Updates symposium; **g)** Expanding BBPD with inclusion of blood/CSF samples and/or neuroimaging; and development of a public resource of sorted cells and omics data from different cell types/regions that differ in vulnerability/resilience to AD pathology (to help us and AAC colleagues and researchers better clarify disease networks, and new treatment targets).

BANNER SUN HEALTH RESEARCH INSTITUTE

Name	Degree	Role
Arce, Richard	--	BBDP Pathology Technician
Arch, Autumn	PhD	Post-Doctoral Fellow, Neuropsychology
Aslam, Sidra	--	Bioinformatics Analyst
Atri, Alireza	MD, PhD	Director, Banner Sun Health Research Institute
Auman, Briana	PysD	Neuropsychologist
Beach, Thomas	MD, PhD	BBDP & Neuropathology Core Director
Beh, Suet Theng	PhD	Postdoctoral Fellow
Belden, Christine	PsyD	Director, Neuropsychology
Borja, Claryssa	--	BBDP Pathology Technician
Brown, Victoria	--	Clinical Research Assistant
Callan, Michael	--	Clinical Research Recruitment Program Manager
Choi, Alexander	MD	Neurologist
Choudhury, Parichita	MD	Physician – Cognitive Disorders & Dementia
Cipriani, Dana L.	--	Clinical Research Representative
Cline, Carol	--	Psychometrist Coord
Cline, Madison P.	--	BBDP Pathology Technician
Davis, Kathryn	--	Psychometrist
Evans, Brittani	--	Neuropsychology Assistant
Glass, Michael	--	BBDP Pathology Technician; Psychometrist
Goldfarb, Danielle	MD	Neuropsychiatrist (dual Neurologist/Psychiatrist)
Guevarra, Cyrus	--	Senior Manager, Sleep Center
Hemmingsen, Spencer	--	BBDP Pathology Technician
Hobgood, Holly M.	--	BBDP Pathology Technician
Intorcica, Anthony	--	Manager, BBDP Pathology Technician
Johnson, Natalie L	--	Clinical Research Assistant
Jones, Jason	--	Polysomnographic Technologist
Keane, Marissa	--	Clinical Research Assistant
Kemperman, Marissa	--	Psychometrist
Krupp, Addison	--	BBDP Pathology Technician
Kuramoto, Angela	RT, MHA	Senior Manager, BBDP & Center for Healthy Aging
Lee-Iannotti, Joyce	MD	Faculty Physician – Neurology/Sleep Medicine
Liebsack, Carolyn	--	Director, Clinical Trials

BANNER SUN HEALTH RESEARCH INSTITUTE

Name	Degree	Role
Long, Kathy E.	--	Clinical Research Representative
Mariner, Monica	--	BBDP Tissue Donation Coordinator
Martinez, Kayleigh	--	BBDP Pathology Technician
McHattie, Rylee	--	BBDP Pathology Technician
Moorley, Naudia	PsyD	Neuropsychologist
Nelson, Courtney	--	BBDP Pathology Technician
O'Connor, Kathy	MS	Longevity Program Coordinator
Orozco, Richard	--	Clinical Research Assistant
Post, Brett	--	Clinical Research Assistant
Qiji, Sanaria	--	Pathology Technician
Rangel, Amy	--	Phlebotomist
Reade, Marina	FNP	Nurse Practitioner, Neurology
Sakhai, Sherwin	--	Post-doctoral Fellow, Neuropsychology
Schmitt, Andrea	BS, CRA	ADRC Administrative Director
Serrano, Geidy	PhD	Director, Civin Laboratory for Neuropathology, BBDP
Shaikh, Farah	--	Clinical Research Assistant
Shprecher, David	DO	Movement Disorders Program Director; Neurologist
Soza, Vanessa	--	Clinical Research Assistant
Stewart, Analisa	--	BBDP Pathology Technician
Suszczewicz, Katie	--	BBDP Pathology Technician
Teran, Marlene	--	Clinical Research Representative
Trncic, Anja	--	Clinical Research Representative
Walker, Jessica	--	Supervisor, BBDP Pathology Technician

BARROW NEUROLOGICAL INSTITUTE
at St. Joseph's Hospital and Medical Center
Institutional Abstract

Barrow Neurological Institute (BNI) at Dignity Health St. Joseph's Hospital and Medical Center is an international leader in the treatment, research and education of brain and spinal diseases, conditions, and injuries. BNI seeks to advance the knowledge and practice of medicine in neuroscience through basic and clinical research, education of medical professionals, and innovation in clinical techniques and technology.

The **Alzheimer's and Memory Disorders Program** at BNI, led by Anna D. Burke, MD, is committed to providing comprehensive clinical care and wraparound services for patients with memory disorders. In addition to clinical care, the program is committed to providing complementary support, education and outreach to Alzheimer's disease patients and caregivers.

In the past year, the program team has led:

- Care partner support groups for Alzheimer's disease (AD), frontotemporal degeneration (FTD), and Lewy body dementia (LBD).
- Memory Cafés, offered in both English and Spanish, that provide safe, stimulating activities for patients and respite for care partners.
- Dementia with Dignity virtual workshop series that provides care partners with information, practical tips, and support to overcome challenging aspects of providing care.
- 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.
- Music, Movement, and Memory classes that include movement exercises, memory and hand-eye coordination games, and other activities.

Under the leadership of Dr. Burke, program clinicians Yonas Geda, MD, Marwan Sabbagh, MD, Amy McLean DNP, 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 2021, program clinicians led 18 active clinical trials. Funding generously matched by the Institute's resources has supported pilot research project awards, including a study designed to develop a novel vaccine that will slow, and hopefully prevent, the development of AD in people with Down syndrome; a study investigating whether simple measures such as slower completion of a finger-tapping test can predict which patients are more likely to progress to AD; and various studies of new approaches to disease-modifying treatments, including monoclonal antibodies against pathological protein targets such as amyloid and p-tau, medications reducing excitotoxicity that will help minimize damage to the brain cells, 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 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 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 focuses 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.

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, was recently awarded funding to examine cognitive decline at the cellular and molecular level in Down syndrome, laying the foundation for a wide range of potential drug interventions that may translate to treatment of AD.

Professor Rita Sattler, PhD, 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) to elucidate the mechanisms of neuronal cell death and is testing novel spine regenerating agents in collaboration with a small biotech company to generate preclinical data sets for future clinical trials. Dr. Sattler is principal investigator and co-investigator of numerous active grants from the NIH/NINDS as well as several disease foundations, including the ALS Association, the Muscular Dystrophy Association, and the Robert Packard Center for ALS Research. This past year, NIH awarded over \$4 million to Dr. Sattler and her team of investigators to fund their research on the role of microglia in ALS and FTD (R01NS120331).

Associate professor Fredric Manfredsson, PhD, research focuses to better understand the role of the protein alpha-synuclein in both healthy cells and those affected by PD. His research also emphasizes understanding the symptomology of the disease, with a focus on the treatment of levodopa-induced dyskinesia and nonmotor symptoms experienced by nearly all patients with PD. Dr. Manfredsson recently received a five-year \$3.2 million dollar grant from NIH to support

his research on a side effect of Parkinson's disease medication known as levodopa-induced dyskinesia.

The **Barrow Neuroimaging Innovation Center** is 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, assistant 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 multiple sclerosis. Dr. Stokes aims to develop advanced imaging biomarkers that can inform on the underlying disease pathophysiology. This year, she has received a five-year \$1.25 million grant award from NIH to study Parkinson's-related changes across different functional networks in the brain using an advanced MRI method.

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	Degree	Role
Ahmad, Saif	PhD	Neuroscientist; Assistant Professor, Translational Neuroscience
Al-Asmer, Jamileh	MBS	Study Coordinator
Baena, Elsa	PhD	Neuropsychologist
Baez Cruz, Jessica	BS	Psychometrist
Bakkar, Nadine	PhD	Neuroscientist; Assistant Professor, Translational Neuroscience
Bergamino, Maurizio	PhD	MR Research, Neuroimaging Innovation Center
Bollam, Padmaja	MD	Psychiatrist
Bowser, Robert	PhD	Chief Scientific Officer; Professor and Chair, Translational Neuroscience
Burke, Anna	MD	Geriatric Psychiatrist; Director, Alzheimer's and Memory Disorders Program
Bustos, Lynette	BS	PhD Graduate Student
Garcia, Angelica	BS	Study Coordinator
Geda, Yonas	MD	Psychiatrist
Gittings, Lauren	PhD	Postdoctoral Fellow
Guerrero, Emyr	BS	Research Assistant
Hanson, Krista	PhD	Neuropsychologist
He, Ben	BS	Molecular Biologist
Keeling, Elizabeth	BS	Data analyst, Neuroimaging Innovation Center
Lorenzini, Ileana	PhD	Postdoctoral Fellow
Mahady, Laura	PhD	Postdoctoral Fellow
Manfredsson, Fredric	PhD	Neuroscientist; Associate Professor, Translational Neuroscience
McCuddy, William T.	PhD	Neuropsychologist
McElvogue, Molly	MS	Data analyst, Neuroimaging Innovation Center
McLean, Amy	DNP	Nurse Practitioner
Medina, David	PhD	Neuroscientist; Assistant Professor, Translational Neuroscience
Moore, Stephen	BS	PhD Graduate Student
Mufson, Elliott	PhD	Neuroscientist; Professor of Neurobiology
Perez, Sylvia	PhD	Neuroscientist; Associate Professor, Translational Neuroscience
Pevey, Ryan	MSc	Neuroscience PhD Student
Prigatano, George	PhD	Neuropsychologist

BARROW NEUROLOGICAL INSTITUTE

Name	Degree	Role
Sabbagh, Marwan	MD	Geriatric Neurologist
Santiago, Jalisa	BS	Clinical Research Assistant
Sattler, Rita	PhD	Neuroscientist; Professor, Translational Neuroscience
Shill, Holly	MD	Neurologist; Director, Muhammad Ali Parkinson Center
Snell, Margeaux	MD	Program Administrator
Steffes, Lori	--	Study Coordinator
Stokes, Ashley	PhD	Neuroscientist; Assistant Professor, Neuroimaging Innovation Center
Townsend, Shaina	BS	Psychometrist
Tran, Chelsea	--	PhD Graduate Student
Tröster, Alexander	PhD	Neuropsychologist

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 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 both 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 disease, by advancing Drug Development Tools (DDTs) for evaluating drug efficacy and safety, working with industry and advocacy organizations to optimize novel clinical trial designs, and aggregating anonymized patient-level data using CDISC consensus standards to facilitate the regulatory review process.

CPAD is collaborating with industry, regulators, academia and philanthropic donors to leverage the wealth of drug development knowledge that the consortium members (industry members as well as academic researchers) possess, by enabling pre-competitive widespread data sharing from clinical trials in AD and contribute directly to the availability of new effective treatments for AD by focusing on the tools and knowledge needed to support successful drug development. By expanding CPAD's existing database and by enabling a rich clinical trial repository, CPAD will contribute directly to the generation of actionable solutions for drug development across the AD continuum. This database will drive the potential for scientific discovery provided by aggregated and standardized primary clinical trial data and resulting quantitative tools will, in turn, provide solutions to optimize the design of clinical trials of AD drugs intended for regulatory review in support of marketing approval.

As of January 2022, CPAD has aggregated data from 57 AD trials, containing nearly 39,000 patient level records spanning fluid and imaging biomarkers, genotypes, demographics, cognitive and functional assessments and other key data elements. The CPAD database has been accessed by over 480 approved applications from 250+ institutions in over 55 countries. The CPAD clinical trial simulation tool, based on CPAD's mild to moderate AD progression model, has been accessed by 140 approved users. Recently acquired AD datasets contain extensive biomarker information, which are key pieces to continue generating actionable solutions and accelerating drug development. Additional datasets will enable continued generation of robust quantitative, model-informed drug development solutions to address key questions and unmet needs in industry and regulatory drug development efforts.

CRITICAL PATH INSTITUTE

Name	Degree	Role
Aggarwal, Varun	PhD	Director, Quantitative Medicine
Akalu, Mussie	MSc	Data Manager, DCC
Cui, Zihan	PhD	Quantitative Medicine Developer
Cullen, Nicholas	--	Modeling & Analysis Intern
Henscheid, Nicholas	PhD	Quantitative Medicine Scientist
Karten, Yashmin	PhD	Associate Director
Lau, Corissa	MBA	Project Manager
Podichetty, Jagdeep	PhD	Director, Quantitative Medicine
Priest, Eileen	--	Project Coordinator
Romero, Klaus	MD	Chief Science Officer, C-Path; Executive Director of Clinical Pharmacology
Sivakumaran, Sudhir	PhD	Executive Director, Critical Path for Alzheimer's Disease (CPAD)
Stafford, Robert	MA	Data Management Team Lead, DCC
White, Hazel	--	Student Intern

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 in which Dr. Caselli serves as the Associate Director as well as Clinical Core Director. The principal institutions involved in this collaborative research effort are Mayo Clinic Arizona (primary site), Banner Alzheimer Institute, Barrow Neurological Institute, Arizona State University, The University of Arizona, and Translational Genomics Research Institute though as the program has matured, it has evolved into a core resource for investigators from these and other institutions as well. Our research program capitalizes on the clinical and neuropsychological expertise of the Behavioral Neurologists and Neuropsychologists at Mayo Clinic Arizona, in conjunction with the genetic expertise of Drs. Eric Klee and Rory Olsen of Mayo Clinic Rochester as well as Drs. 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 MRI's on more than 150 members and whole genome sequencing on the 527 members of this cohort for who 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.

Our longitudinal study design is a unique strength with our longest participants having been followed for nearly 25 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 during our 50's in APOE e4 carriers, 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.

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 progression from preclinical Alzheimer's disease to MCI, and from MCI to dementia
3. developing a personalized predictive model based on genomic and other preclinical parameters for the timing of clinical progression
4. informing the design of primary and secondary prevention clinical trials
5. providing a core resource to all our collaborative partners
6. correlating non-traditional measures of neuropsychiatric status such as intellectual achievement, sleep patterns, and personality factors with preclinical cerebral amyloid levels
7. determining 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 clinical progression.
8. contributing to the development of a personalized, inexpensive, and widely accessible diagnostic based on EEG through a deep learning approach in collaboration with an industry sponsor.

This research proposal has been peer reviewed and approved by the Mayo Clinic Institutional Review Board (IRB #259-99).

MAYO CLINIC ARIZONA

Name	Degree	Role
Adler, Charles H.	MD, PhD	Neurologist
Baxter, Leslie C.	PhD	Neuroimaging Scientist
Brostrom, Debra	BA	Study Coordinator
Caselli, Richard J.	MD	Principal Investigator, Clinical Core Director, Associate Director, Behavioral Neurologist
Caviness, John N.	MD	Neurologist
Dueck, Amylou C.	PhD	Biostatistician
Driver-Dunckley, Erika D.	MD	Neurologist
Dumitrascu, Oana M.	MD	Vascular Neurologist
Ezenne, Adaeze	NP	Nurse Practitioner
Fryer, John D.	PhD	Neuroscientist
Henslin, Bruce	BA	Study Coordinator
Langlais, Blake	MS	Biostatistician
Locke, Dona E.	PhD	Co-Investigator, Neuropsychologist
Mehta, Shyamal H.	MD, PhD	Neurologist
Wicklund, Meredith R.	MD	Co-Investigator, Behavioral Neurologist
Woodruff, Bryan K.	MD	Co-Investigator, Behavioral Neurologist
Zhang, Nan	MS	Biostatistician

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. There are also 13 additional programs including new Precision Medicine and Master of Public Health Programs. 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 (both human and veterinary) are involved in many different research efforts, with collaborations throughout Arizona and the US. 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. 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 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 understanding, patient evaluation and treatment mechanisms, education and outreach, and clinical recruitment.

Current Alzheimer's research-related activities at Midwestern include:

- 1) Understanding the potential role of microbes in the development of Alzheimer's disease 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) cell culture models of neuronal infection with microbes previously identified as being present in AD patients, and 3) infection of 3xTG and APOE4 mice to test if infection with common microbes can exacerbate pathology in these models. 4) Evaluation of gut microbiome changes in 3xTg and APOE3/4 mice

- 2) Determining the ability of genistein and exercise to (1) reverse inflammatory state, (2) modify brain protein expression, (3) modify gut leakiness, (4) modify microbiome, (5) reverse diabetic obesity, and (6) improve bone health in mice fed a high fat diet (HFD). The goal of this project is to examine the link between metabolic syndrome and dementia, and to test a drug which may be useful for modifying the cognitive outcome in patients.
- 3) Evaluating the effectiveness of music intervention to increase or maintain quality of life for patients with dementia. Study participants are being evaluated for reductions in behavioral and psychological symptoms.
- 4) Developing and validating new pharmacological treatments, such as norclozapine, that could have a positive impact on Alzheimer's disease and other neurological conditions, and support research on the cellular- and subcellular-targeted delivery of relevant treatments.
- 5) Evaluating the dysfunction within and contribution of various neurotransmitter systems in Alzheimer's disease and related disorders, such as Parkinson's disease, prominently including the nicotinic and muscarinic receptor systems of the brain.
- 6) Examining a proposed link between a protein that protects the chromosome ends against shortening (RAP1) and a protein localized to astrocytes (GFAP δ), 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 GFAP δ variants will modulate the accumulation of amyloid deposits in a cell culture model.
- 7) Applying geroscience to the study of Alzheimer's disease by evaluating whether cellular senescence can be mitigated by intermittent fasting. This study is being done in senescence-accelerated mice.
- 8) Studying the regulation of neuronal gene expression by the telomere protection protein RAP1 and the demethylase TET3.
- 9) Screening for human proteins that affect amyloid beta peptide production by gamma secretase.
- 10) Examining the involvement of inflammatory molecules in the pathophysiology of Alzheimer's disease, related disorders, and CNS injury.
- 11) Determining whether elevated APOE4 expression is linked to cerebrovascular dysfunction in in young and aged APOE4 mice, by measuring middle cerebral artery (MCA) function in APOE3 and APOE4 mice.
- 12) Studying exercise induced mitigation of cellular senescence as a peripheral control mechanism for Alzheimer's disease using a senescence-accelerated SAMP8 mouse model.
- 13) Studying the role of vitamin B12 deficiency in creating vulnerability to neurological disease using stroke outcome as a measure in aged mice.

MIDWESTERN UNIVERSITY

Name	Degree	Role
Abel, Kelsey	BS	Technician
Al-Nakkash, Layla	PhD	Principal Investigator
Anderson, Sarah	MOT/OTR	MAAC Investigator
Bae, Nancy	PhD	Principal Investigator
Broderick, Thomas	PhD	Principal Investigator
Call, Gerald	PhD	MAAC Investigator
Castro, Monica	BS	Technician
Christensen, Stephanie	PhD	MAAC Investigator
Chu, Ping	BS	Technician
Delgado Flint, Melissa	PsyD	MAAC Investigator
Eckman, Delrae	PhD	MAAC Investigator
Esfandiarei, Mitra	PhD	MAAC Investigator
Fitzgerald, Nancy	DDS	MAAC Investigator
Gonzalez, Fernando	PhD	Principal Investigator
Haley, Nick	PhD	MAAC Investigator
Halket, Christine	DDS	MAAC Investigator
Hernandez, Jose	PhD	MAAC Investigator
Huang, Vanthida	PharmD	Co-Investigator
Hull, Elizabeth	PhD	MAAC Investigator
Jadavji, Nafisa	PhD	Principal Investigator
Jentarra, Garilyn	PhD	Administrative PI, Project Principal Investigator
Jones, Carleton	PhD	MAAC Investigator
Jones, Douglas	PhD	Co-Investigator
Jones, T. Bucky	PhD	Principal Investigator
Kaufman, Jason	PhD	MAAC Investigator
Knudsen Gerber, Dawn	PharmD	MAAC Investigator
Korch, Shaleen	PhD	MAAC Investigator
Kozlowski, Michael	OD, PhD	MAAC Investigator
Lawson, Kathy	PhD	Co-Investigator
Lee, Seungyong	PhD	MAAC Investigator
Leyva, Kathryn	PhD	MAAC Investigator
Li, Weidang	PhD	MAAC Investigator

MIDWESTERN UNIVERSITY

Name	Degree	Role
Olsen, Mark	PhD	MAAC Investigator
Pagan, Misty	DNP, APRN	MAAC Investigator
Potter, Pamela	PhD	Co-Investigator
Potter, Ross	PhD	Laboratory Manager
Revill, Ann	PhD	MAAC Investigator
Rogers, Alexandra	BS	Technician
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	Principal Investigator
Yevseyenkov, Vladimir	OD, PhD	MAAC Investigator

NORTHERN ARIZONA UNIVERSITY

The Pathogen and Microbiome Institute (PMI) is based at Northern Arizona University (NAU). 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 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 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 a 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 diagnostics or predictors of AD that can be used to delay or prevent the onset of this devastating diagnosis. 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 at Northern Arizona University is well-positioned to achieve these goals. Dr. Cope has extensive experience with transcriptome analysis and host-microbiome interactions, and Dr. Caporaso is an expert in microbiome analysis, including recent work on using fecal microbiota transplant to improve behavioral symptoms of autism in a Phase 1 clinical trial. In addition to our laboratory and sequencing capacity, we are developing laboratory and bioinformatics best practices for microbiome research. This includes automated nucleic extraction methods, application and validation of the latest microbiome sequencing protocols, and development of QIIME 2 (led by PI Caporaso), a microbiome bioinformatics platform. A new feature implemented in QIIME2 is provenance replay, which will allow investigators to exactly reproduce an analysis performed in a published study. This was recently used in a pre-print resulting directly from AAC funds (<https://doi.org/10.21203/rs.3.rs-1538737/v1>) and is being prepared for publication. We are therefore uniquely positioned to advance knowledge of the relationship between the gut microbiota and AD. These goals are achieved through decentralized data provenance tracking wherein each step of the analysis is automatically recorded and easily obtained in the results.

NORTHERN ARIZONA UNIVERSITY

Name	Degree	Role
Barroso, Daisy	--	Undergraduate Researcher
Borsom, Emily	BS	Graduate Student
Caporaso, J Gregory	PhD	PI
Conn, Kathryn	BS	Graduate Student
Cope, Emily	PhD	PI and Project Director
Dillon, Matthew	MS	Research Software Engineer
Herman, Chloe	BS	Graduate Student
Keefe, Chris	--	Student Research Software Engineer
Keim, Paul	PhD	Executive Director, PMI
Lee, Keehoon	PhD	Postdoctoral Scholar
Schwartz, Egbert	PhD	Co-I
Testo, George	--	Undergraduate Researcher

TRANSLATIONAL GENOMICS RESEARCH INSTITUTE

The Translational Genomics Research Institute (TGen, a part of City of Hope) 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), DNA and RNA sequencing studies involving multiple brain cell types and regions in the brain donors with and without AD (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 before the onset of symptoms, leverage molecular information to identify novel drug targets, and gain a deeper understanding of the genomic changes associated with disease onset and progression.

Over the past year, researchers at TGen have achieved extraordinary successes in numerous AD and aging research programs, some of the most notable being:

MindCrowd: In 2013, Drs. Huentelman at TGen and Ryan and Glisky at the University of Arizona launched MindCrowd, a unique online research study aimed at identifying factors that inform how the healthy brain works. Researchers have used data collected from nearly 300,000 participants to learn more about how demographic, health, medical, and lifestyle factors affect cognition throughout the lifespan. In June 2022, MindCrowd 2.0 was launched, adding new “brain game” tests and allowing users to join the project using their smartphone, a capability that will help reach more people who are often underrepresented in studies of cognition and aging.

Precision Aging Network: The updates to MindCrowd were made possible in part by a 5-year, \$60 million grant from the National Institutes of Health for the Precision Aging Network, a major research project to better understand how and why people experience brain aging differently. Led by researchers at the University of Arizona, the network includes scientists at TGen, Arizona State University, Emory University, Johns Hopkins University, Baylor College of Medicine, the Georgia Institute of Technology, and the University of Miami. TGen leads two project and one core within the Precision Aging Network.

Blood-Based Clues of Parkinson’s Disease: Working with collaborators at the Michael J. Fox Foundation for Parkinson’s Research, University of Southern California and the National Institute on Aging, researchers at TGen completed a comprehensive RNA transcriptomic resource from whole blood samples for use by the Parkinson’s research community for biomarker development. Using the resource’s data, TGen researchers discovered immune system alterations could provide a path for future diagnostics and studies of this progressively debilitating neurological disease.

As a result of continuing support from the AAC, state of Arizona and other sponsors, scientists have begun to capitalize on important collaborations between TGen and Northern Arizona University at TGen North, home of the Pathogen & Microbiome Division. Led by Dr. David Engelthaler, TGen North focuses on diagnostic, analytic, forensic, ecologic, and epidemiologic research of microbes that are of interest to medicine and public health. Recently announced, the TGen Integrated Microbiomics Center (TIMC), will house state-of-the-art sequencing technologies and bioinformatic tools to provide high-quality microbiome analysis services to academic and industry researchers.

TRANSLATIONAL GENOMICS RESEARCH INSTITUTE

Name	Degree	Role
Alsop, Eric	PhD	Computational Scientist
Antone, Jerry	BS	Research Associate
De Both, Matthew	BS	Bioinformatician
Glosh-Halder, Tithi	PhD	Postdoctoral Fellow
Huentelman, Matthew	PhD	Principal Investigator
Lechuga, Cynthia	MBA	Sr. Grants & Contract Administrator
Moore, Bethine	BA	
Piras, Ignazio S.	PhD	Investigator, Neurogenomics
Robles, Laura	MBA	Project Accountant
Sharma, Sunil	MD,PhD, FACP,MBA	Co-Investigator
Soldi, Raffaella	PhD	Co-Investigator
Schork, Nicholas	PhD	Investigator, Quantitative Medicine
Van Keuren-Jensen, Kendall	PhD	Co-Investigator

UNIVERSITY OF ARIZONA

Researchers at the University of Arizona (UA) are engaged in collaborative, multi-disciplinary programs 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 cognitive aging and dementia. To accomplish these goals, UA investigators representing colleges, departments and institutes from across the campus that encompass the fields of neuroimaging, biomedical engineering, cognitive and behavioral neurosciences, neuropsychology, psychiatry, neurology, cardiology, pharmacology, physiology, and statistics are involved in these research programs. Projects apply a range of scientific approaches from basic neuroscience to cognitive science to clinical intervention in studies that translate across human and non-human animal models of aging and age-related disease. A major emphasis in this research is the development and utilization of magnetic resonance imaging (MRI) methods to measure brain structure, function, and connectivity in aging and age-related neurodegenerative disease. Novel MRI methods and image analysis pipelines not only benefit researchers at UA, but they are also made available to the entire neuroimaging community.

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: 1) investigating the neural systems and associated cognitive processes that are altered in the context of aging and age-related disease, 2) tracking brain changes and cognitive abilities during the course of aging, 3) evaluating how genetic, health, and lifestyle factors influence brain aging and cognitive decline, 4) developing novel biomarkers to improve early detection of brain and cognitive changes due to aging and age-related diseases, 5) understanding cellular mechanisms of brain aging in animal models, and 6) identifying and testing novel interventions to improve cognitive functioning and decrease risk for AD, and 6) developing libraries and repositories for data sharing, including open-source pipelines for image analysis.

The AAC pilot project program at UA continues to be highly successful in leading to influential publications in high impact journals and extramural grant funding from NIA, NIH, ABRC, NCI, NIBIB, DOD, NIDA, NINDS, NIGMS, and the Flinn Foundation. **Most notably, in the past year UA researchers were awarded a \$60 million grant from NIA to establish the Precision Aging Network, with the goal of closing the gap between cognitive health span and human lifespan (NIA, Barnes, Ryan, Hay, Brinton).** Researchers from the University of Arizona, Arizona State University, Emory University, Johns Hopkins University, Baylor College of Medicine, the Georgia Institute of Technology, the University of Miami and the Translational Genomics Research Institute will be part of the UArizona-led network. The program will embark on four national-scale research studies designed to better understand the neural mechanisms that account for optimal brain performance in older age and those that underlie age-related cognitive impairment and disorders such as Alzheimer's disease.

Researchers at the University of Arizona Health Sciences have also spearheaded success of The University of Arizona-Banner Health All of Us Research Program, which met a significant milestone this year, enrolling over 50,000 participants who provide their EHR data and biological specimens including over 75% from Latino and other under-represented groups. The program aims to build one of the largest and most diverse databases of health information of its kind and allowing researchers to use the data to study thousands of diseases. All of Us UArizona-Banner leads the nation in enrollment in this important health initiative.

UArizona Health Sciences is also one of more than 30 research teams across the country participating in the NIH Researching COVID to Enhance Recovery initiative, known as RECOVER, which seeks to understand, treat and prevent the long-term effects of COVID-19.

Other notable recent grants include:

- Stimulating brain function in older adults at risk for AD using near-infrared photobiomodulation (NIA, Alexander).
- Understanding the impact of sedentary lifestyle on risk for AD in middle aged and older adults (NIA, Alexander).
- Evaluating the impact of extracranial carotid atherosclerosis on cognitive impairment (NIA, Weinkauff, Alexander).
- Preserving memory circuits in normal aging through NPTX2 (NIH/NIA, Barnes).
- Enhancing hippocampal plasticity using repetitive transcranial magnetic stimulation (NIA, Chou).
- Evaluating the mechanisms of decision making in older adults (NIA, Wilson).
- 4D transcranial acoustoelectric imaging for high resolution functional mapping of neuronal circuits (NIBIB, Cowen).
- IND enabling studies for a novel Mas receptor agonist for treatment of vascular dementia (NIH/NIA, Hay, Ryan).

This program of research is strengthened by our close ties to other research units at UA including the **Evelyn F. McKnight Brain Institute**, studying the longitudinal effects of aging on memory processes in older adults with and without increased risk for AD, and the **Center for Innovation in Brain Sciences**, focusing on the development of pharmacological interventions for degenerative brain diseases. UA researchers participate in complementary efforts to support the Arizona ADRC with recruitment and longitudinal follow up of individuals with mild cognitive impairment, AD, and other forms of dementia. 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. Program-related activities at the UA over the past year include several major areas of research:

MRI methods, image analysis, and shared resources.

Over the past few years, we continue to build the resources required for sharing standardized measurements that are to be made available to the research community, utilizing XNAT, a shared online repository for neuroimaging data that is funded by the NIH. The complexity and high cost of collecting large-scale datasets highlights the importance of sharing data across laboratories. The database will include neuropsychological, neuroimaging, and biospecimen data obtained from well-characterized older adults. Standardized pipelines for MRI data analysis have also been successfully established.

Our researchers continue to develop and implement new MRI techniques and statistical analysis methods that may prove useful in examining brain structure, function, connectivity, and pathology in both human and non-human animal models of aging and age-related disease. MRI methods including high-resolution structural imaging, fMRI, diffusion, perfusion, and resting state connectivity are being utilized to better understand the neural basis of memory and other cognitive changes across the normal adult lifespan, and compensatory or adaptive strategies that lead to better memory function. Over the past year, relevant pilot studies have:

- employed new algorithms for identifying cognitively significant silent brain infarcts (CS-SBIs) on MRI, identifying the characteristics of SBIs that affect cognition and determining the impact of cerebral blood flow and patterns of brain connectivity on SBIs and cognitive changes,
- improved the acquisition and analysis of Diffusion Magnetic Resonance Imaging (dMRI) by implementing deep learning (DL) analysis techniques and incorporating more advanced diffusion models, and evaluating the DL-dMRI approach in different cohorts to measure its impact on subsequent detection/classification tasks,

- employed network-based statistics (NBS) and graph-based statistics (GBS) to identify neuronal network signatures that significantly differ between AD and control groups, and identify network signatures that are correlated with the cognitive performance and disease progression, utilizing neuroimaging data obtained from the ADNI database,
- developed and evaluated MRI protocols to enable hippocampal mean apparent propagator (MAP)-MRI, multi-spin-echo (MSE) and selective inversion recovery (SIR) *in-vivo* to achieve high-resolution and high-quality microstructural MRI maps of hippocampal subfields, and establish a robust processing pipeline for hippocampal subfield measurements of MAP-MRI metrics, myelin water fraction (MWF) and bound pool fraction (BPF),
- expanded resources for MRI data sharing and pipelines for standardized state-of-the-art MRI analyses in order to increase access to imaging resources for researchers throughout the Arizona Alzheimer's Consortium, to disseminate information on MRI resources at UA, and to increase interaction with scientists engaged in imaging research and image analysis at other AAC sites across the state and the broader research community, and
- created a data management and annotation system to support imaging data, in addition to software pipelines for data harmonization, pre-processing, and analysis of imaging data.

Cognitive aging and risk factors for AD. A major theme of our research continues to focus on understanding the individual trajectories of normal aging and the early detection of cognitive impairments associated with aging and Alzheimer's disease (AD). Over the past year, multiple projects focused on identifying and understanding the factors that increase risk for age-related cognitive impairment and AD, including:

- identifying the effects of white matter lesions on frontal cortex and executive functions in healthy older adults and how frontal control networks are related to executive function in healthy aging,
- performing probabilistic tractography analyses on diffusion tensor MRI to isolate subcortical white matter tracts for quantitative analyses with respect to age, cognitive, and sensory status in 12 macaques ages 15 to 32, using refined methods for registering *ex vivo* MRI data with histologically prepared brain sections in the macaque.
- identifying the characteristics of microembolisms after carotid revascularization that affect cognition and determining the impact of changes in cerebral blood flow on microembolisms and cognitive functioning among older adults,
- **determining how post-recovery cognitive functioning and brain structure/function relates to COVID-19 severity in older adults measured by the presence of respiratory symptoms and hospitalization with ARDS and levels of circulating neurofilament light protein, particularly on cognitive tests that are mediated by hippocampal function, and**
- creating sensitive assays in blood and urine to identify biomarkers for disease diagnostics, using quantification of serum matrix effects on FLOWER, an ultra-sensitive optical sensing technology, to compare known spiked concentrations of A β 42 in serum with the recovered concentration using FLOWER, and verifying the selectivity of the sensing system for A β 42 over other commonly found biomolecules in serum.

Neural mechanisms and interventions. Researchers at UA are studying various potential targets for intervention and neuroprotective mechanisms. Each study has the potential to lead to novel interventions that may decrease risk for AD, slow the progression of the disease, and ameliorate cognitive impairments associated with normal aging and AD. Other studies are implementing treatments to obtain preliminary data on safety and efficacy. These include:

- determining the effect of astrocytic mitochondrial dysfunction on the hippocampal transcriptome, synaptic function, and neuroinflammation, and how dysfunctional astrocytic mitochondria might reprogram the brain's metabolic profile,
- developing an orally dosable, metabolically stable, brain-penetrant BDNF-mimicking TrkB agonist, by designing and synthesizing a series of GSB-106 peptide analogs and small molecule mimetics, and comparing the pharmacology of our BDNF-mimicking TrkB agonists to BDNF in a TrkB activation assay,
- employing the novel Neuropixels system, a recording system that allows measurement from >1000 neurons, to collect large ensemble data from hippocampal subregions (CA3, CA2, and CA1) and prefrontal subregions (anterior cingulate, prelimbic, and infralimbic) in young and aged rats during learning (an associative learning task) and sleep,
- determining if treatment with Angiotensin (1-7) in participants with heart failure at high risk for VCID/ADRD improves cognitive functions measured as a change in performance from baseline to follow up on memory, executive functioning, language and processing speed in the Angiotensin (1-7) treatment groups compared to placebo controls,
- determining the efficacy of MRI-guided accelerated repetitive transcranial magnetic stimulation compared to sham treatment to ameliorate memory performance among older adults with mild cognitive impairment,
- evaluating the effectiveness of individualized fMRI-guided transcranial direct current stimulation (tDCS) on language recovery in individuals with AD and primary progressive aphasia, compared to sham treatment, and
- investigating the effect of a novel antibody therapy in mice that targets toxic forms of alpha-synuclein, comparing efficacy between antibody therapy given with and without prior BBB opening via a novel method, MRI-guided focused ultrasound.

UNIVERSITY OF ARIZONA

Name	Degree	Role
Altbach, Maria	PhD	Investigator; Biomedical Engineering, Medical Imaging
Alexander, Gene	PhD	Investigator; Psychology, Psychiatry, Neuroscience, Evelyn F. McKnight Brain Institute
Andrews-Hanna, Jessica	PhD	Investigator, Psychology and Evelyn F. McKnight Brain Institute
Barnes, Carol	PhD	Investigator; Psychology, Neurology, Neuroscience, Evelyn F. McKnight Brain Institute
Beeson, Pelagie	PhD	Investigator; Speech, Language and Hearing Sciences, Neurology
Bilgin, Ali	PhD	Investigator; Biomedical Engineering, BIO5 Institute, Medical Imaging
Brinton, Roberta	PhD	Investigator, Center for Innovation in Brain Science, Pharmacology, Neurology, Psychology, Evelyn F. McKnight Brain Institute
Chang, Rui	PhD	Investigator, Neurology
Chen, Nan-Kuei	PhD	Investigator, Biomedical Engineering
Chou, Ying-hui	PhD	Investigator, Psychology and Evelyn F. McKnight Brain Institute
Cowen, Stephen	PhD	Investigator; Psychology
Fisher, Julia	PhD	Investigator; Biomedical Informatics & Biostatistics
Gaffney, Kevin	PhD	Investigator; Pharmacology
Grilli, Matthew	PhD	Investigator, Psychology and Evelyn F. McKnight Brain Institute
Hsu, Chiu-Hsieh	PhD	Investigator; Public Health
Hay, Meredith	PhD	Investigator; Physiology, Psychology, Evelyn F. McKnight Brain Institute
Hernandez, Gerson	MD, MPH	Investigator, Center for Innovation in Brain Science
Hoscheidt, Siobhan	PhD	Investigator, Psychology
Hutchinson, Elizabeth	PhD	Investigator; Biomedical Engineering
Khanna, May	PhD	Investigator, Center for Innovation in Brain Science
Konhilas, John	PhD	Investigator, Biomedical Engineering, Physiology
Kielar, Aneta	PhD	Investigator; Speech, Language and Hearing Sciences
Kuo, Phillip	MD, PhD	Investigator; Biomedical Engineering, Medical Imaging
Parthasarathy, Sairam	MD	Investigator; Medicine
Pires, Paulo	PhD	Investigator; Physiology
Raichlen, David	PhD	Investigator; Anthropology
Raikes, Adam	PhD	Investigator, Center for Innovation in Brain Science
Rodgers, Kathleen	PhD	Investigator, Center for Innovation in Brain Science
Rouse, Andrew	PhD	Investigator, Medical Imaging

UNIVERSITY OF ARIZONA

Name	Degree	Role
Ryan, Lee	PhD	Investigator; Psychology, Neurology, Neuroscience Program, Evelyn F. McKnight Brain Institute
Sweitzer, Nancy	MD, PhD	Investigator; Medicine, UArizona Health Sciences
Su, Judith	PhD	Investigator, Optical Sciences, Chemistry and Biochemistry
Trouard, Theodore	PhD	Investigator; Biomedical Engineering, Medical Imaging, Evelyn F. McKnight Brain Institute
Vitali, Francesca	PhD	Investigator; Neurology, Center for Innovation in Brain Science
Weinkauf, Craig	MD, PhD	Investigator, Surgery
Yin, Fei	PhD	Investigator, Center for Innovation in Brain Science
Zhou, Wei	MD	Investigator, Vascular Surgery

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, Phoenix VA Health Care System, and Phoenix Children's. 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	Degree	Role
Fanous, Ayman	MD	Chair, Department of Psychiatry
Gallitano, Amelia	MD, PhD	Professor
Giordano, Katherine R.	BS	CTS Graduate student
Griffiths, Daniel R.	BS	Research Specialist, Senior
Irwin, Chase	MS	Biostatistician
Leighty, Connor R.	BS	CTS Masters student
Lifshitz, Jonathan	PhD	Principal Investigator, Professor
McQueen, Kyli A.	BS	Research technician
Migrino, Raymond Q.	MD	Clinical Professor
Rangan, Pooja	MBBS, MPH	Assistant Research Professor
Rojas Valencia, Luisa M.	MS	CTS Graduate student
Tallent, Bret R.	LATG	Laboratory manager
Thomas, Theresa Currier	PhD	Associate Professor



PROJECT PROGRESS REPORTS

**ARIZONA STATE UNIVERSITY
PROJECT PROGRESS REPORTS**

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Comparison of age-related responses to menopause variations on brain functioning: A focus on cognitive outcomes. Heather Bimonte-Nelson, PhD (PI), Melissa Wilson, PhD (Co-I), Julia A. Files, MD, FACP, NCMP. Arizona State University; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

The specific aim of this project is to determine whether age at hysterectomy impairs cognition. This project corresponds with the sister project by PI Dr. Wilson. Reproductive and brain tissues will be allocated to the laboratory of Dr. Wilson to study molecular mechanisms (as described in her application). To follow, putative relationships between reproductive and brain tissues with behavioral outcomes will be analyzed. Moreover, Dr. Julia Files, a physician and Professor of Medicine in the Division of Women's Health, Department of Internal Medicine at Mayo Clinic, Scottsdale, will be our collaborator and critical discussant. She will give us insight into the clinical menopausal population to ensure that we are as translational as possible in our questions and interpretations once brain, uterus, and behavior data are collected.

Background and Significance:

In the United States, between 1998 and 2010, over 7.4 million women underwent hysterectomy, or the surgical removal of the uterus, with approximately 600,000 surgeries occurring each year (Carlson et al., 1993; Corona et al., 2015, Wright et al., 2013). Of these surgeries, up to seventy percent of hysterectomies are performed in women under the age of 50, and this is before the average age of menopause (Wright et al., 2013). Hysterectomy is one of the most common surgical interventions in women, second only to cesarean section (CDC, 2010; Carlson et al., 1993). Hysterectomy is most often given to alleviate undesirable symptoms related to benign uterine conditions.

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 sudden loss of ovarian hormones resulting from oophorectomy prior to natural reproductive senescence can be detrimental to memory 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). Notably, the surgical removal of the uterus alone does not result in the same drastic loss of circulating ovarian hormones that occurs with oophorectomy.

Whether hysterectomy impacts brain functioning differently in young adulthood versus older age is a critically important clinical question that has not yet been systematically evaluated in women or animal models. Clinical work indicates that there is an increased relative risk ratio for developing early onset dementia for women who underwent hysterectomy with and without oophorectomy compared to women with no history of hysterectomy; this increased risk was particularly evident when the women had a hysterectomy before the age of 30 years (Phung et al., 2010). There is also research demonstrating that hysterectomy prior to natural reproductive senescence can initiate ovarian failure earlier (Kaiser et al., 1989). Notably, there was a greater risk of dementia when surgical menopause (i.e., ovary removal with or without hysterectomy) occurred before the natural transition menopause (Rocca et al., 2007, 2012). Yet, others have demonstrated that Alzheimer's disease (AD) risk decreased with hysterectomy, with or without oophorectomy. Of note, the majority of the women in this study were over 51 years of age, and therefore likely post-menopausal at the time of hysterectomy surgery (Imtiaz et al., 2014). The

collected findings thus far, while not completely concordant, indicate that even with ovarian preservation hysterectomy alters brain function in women, and that these effects are impacted by age at surgery. It therefore follows that hysterectomy could be an important factor for understanding healthy cognitive aging. We have shown hysterectomy-induced impairments in young animals after a short-term time period of six weeks (Koebele et al., 2019). The current application systematically tests whether the effects of short-term hysterectomy present in old age as well. Moreover, we will establish a new collaboration with Dr. Melissa Wilson to yield novel mechanistic information about brain behavior-hormone-uterus relationships via gene expression assessments.

Proposed One-Year and Long-Term Outcomes:

Rats will be ordered, and surgeries and behavior testing will be completed by the end of the one-year project period. We plan to 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 two years from study initiation, and a grant to study brain/behavior/aging/hormone relationships with hysterectomy. Regarding analyses of uterine and brain tissues, we plan to establish a new collaboration with the laboratory of Dr. Wilson to identify potential mechanistic information that could identify new relationships and drivers for changes observed in both the uterus and brain following ovarian modulation; such work will aid in characterizing these two critical structures across the trajectory of female aging. These outcomes will be the focus of a future collaborative NIH grant, which will take a systems approach to further understand reproductive health and brain function, with an eye toward the development of clinical therapeutics to optimize health outcomes for women across the lifespan.

Year End Progress Summary:

Rats were ordered and surgeries have been performed. In addition, behavioral testing has been completed, with results replicating prior hysterectomy cognitive results in younger animals, and now additionally showing that cognitively-impairing effects are also present when surgery is performed at later ages. The collaboration with Dr. Wilson has also ensued as described and as planned. Our laboratory teams have had joint meetings and together, we have collected tissues from behaviorally tested animals. As described, these tissues are being processed and analyzed by Dr. Wilson's team to be correlated with behavioral outcomes. This latter portion of the aim is currently being undertaken. It has been a wonderful, productive collaboration thus far, and we are grateful to the Arizona Alzheimer's Consortium for the resources to initiate this novel collaborative relationship. We are excited to see where the future data will lead us as we move forward.

We have received monies from the Arizona Alzheimer's Consortium in the last two years. Papers in the last two years are as follows (including review papers which incorporated findings from the support); these papers include acknowledgments to the AAC: **+denotes graduate or postdoc student in lab; ^denotes undergraduate student in lab**

1. +Koebele, S.V., Nishimura, K.J., **Bimonte-Nelson, H.A.**, Kemmou, S., Ortiz, J.B., Judd, J.M., Conrad, C.D. (2020) A long-term cyclic plus tonic regimen of 17 β -estradiol improves the ability to handle a high spatial working memory load in ovariectomized middle-aged female rats. *Hormones and Behavior*. 118. doi: 10.1016/j.yhbeh.2019.104656. PMID: 31862208
2. Gipson, C.D. & **Bimonte-Nelson, H.A.** (2020) Interactions between reproductive transitions during aging and addiction: promoting translational crosstalk between different fields of research. *Behav Pharmacol*. PMID: 32960852 doi: 10.1097/FBP.0000000000000591
3. +Prakapenka, A.V., +Peña, V.L., ^Strouse, I., Northup-Smith, S., ^Schrier, A., ^Ahmed, K., **Bimonte-Nelson, H.A.**, Sirianni, R.W. (2020) Intranasal 17 β -estradiol modulates spatial

- learning and memory in a rat model of surgical menopause. *Pharmaceutics*, 12(12). PMID: 33348722 doi: 10.3390/pharmaceutics12121225
4. +Prakapenka, A.V., ^Quihuis, A.M., ^Carson, C.G., ^Patel, S., **Bimonte-Nelson, H.A.**, Sirianni, R.W. (2020) Encapsulated 17 β -estradiol improves spatial memory and increases uterine stimulation in middle-aged ovariectomized rats. *Front Behav Neurosci*, 14. PMID: 33424559 doi: 10.3389/fnbeh.2020.597690
 5. +Koebele, S.V., +Mennenga, S.E., ^Poisson, M.L., ^Hewitt, L.T., ^Patel, S., Mayer, L.P., Dyer, C.A., **Bimonte-Nelson, H.A.** (2020) Characterizing the effects of tonic 17 β -estradiol administration on spatial learning and memory in the follicle-deplete middle-aged female rat. *Horm Behav*, 126. PMID: 32949557 doi: 10.1016/j.yhbeh.2020.104854
 6. Maher E.E., Overby P.F., Bull A.H., Beckmann J.S., Leyrer-Jackson J.M., +Koebele S.V., **Bimonte-Nelson H.A.**, Gipson C.D. (2021) Natural and synthetic estrogens specifically alter nicotine demand and cue-induced nicotine seeking in female rats. *Neuropharmacology*, 198:108756. doi: 10.1016/j.neuropharm.2021.108756. Epub 2021 Aug 17. PMID: 34416269; PMCID: PMC8484059.
 7. Zeibich L., +Koebele S.V., +Bernaud V.E., Ilhan Z.E., Dirks B., Northup-Smith S.N., ^Neeley R., Maldonado J., Nirmalkar K., Files J.A., Mayer A.P., **Bimonte-Nelson H.A.**, Krajmalnik-Brown R. [***Bimonte-Nelson and Krajmalnik-Brown share senior authorship***] (2021) Surgical menopause and estrogen therapy modulate the gut microbiota, Obesity Markers, and Spatial Memory in Rats. *Front Cell Infect Microbiol*. 11:702628. doi: 10.3389/fcimb.2021.702628. PMID: 34660336; PMCID: PMC8515187.
 8. Stonebarger G.A., **Bimonte-Nelson H.A.**, Urbanski H.F. (2021) The rhesus macaque as a translational model for neurodegeneration and Alzheimer's disease. *Front Aging Neurosci*, 13:734173. doi: 10.3389/fnagi.2021.734173. PMID: 34539388; PMCID: PMC8446616.
 9. +Koebele S.V., +Hiroi R., ^Plumley Z.M.T., ^Melikian R., +Prakapenka A.V., ^Patel S., ^Carson C., ^Kirby D., +Mennenga S.E., Mayer L.P., Dyer C.A., **Bimonte-Nelson H.A.** (2021) Clinically used hormone formulations differentially impact memory, anxiety-like, and depressive-like behaviors in a rat model of transitional menopause. *Front Behav Neurosci*, 15:696838. doi: 10.3389/fnbeh.2021.696838. PMID: 34366807; PMCID: PMC8335488.
 10. Koebele S.V., Quihuis A.M., Lavery C.N., Plumley Z.M.T., Castaneda A.J., **Bimonte-Nelson H.A.** (2021) Oestrogen treatment modulates the impact of cognitive experience and task complexity on memory in middle-aged surgically menopausal rats. *J Neuroendocrinol*, 33(9):e13002. doi: 10.1111/jne.13002. PMID: 34378820.
 11. Gipson C.D., **Bimonte-Nelson H.A.** (2021) Interactions between reproductive transitions during aging and addiction: promoting translational crosstalk between different fields of research. *Behav Pharmacol*, 32(2&3):112-122. doi: 10.1097/FBP.0000000000000591. PMID: 32960852; PMCID: PMC7965232.
 12. +Bernaud V.E., Hiroi R., Poisson M.L., Castaneda A.J., Kirshner Z.Z., Gibbs R.B., **Bimonte-Nelson H.A.** (2021) Age impacts the burden that reference memory imparts on an increasing working memory load and modifies relationships with cholinergic activity. *Front Behav Neurosci*, 15:610078. doi: 10.3389/fnbeh.2021.610078. PMID: 33643006; PMCID: PMC7902531.
 13. George A.A., Vieira J.M., Xavier-Jackson C., Gee M.T., Cirrito J.R., **Bimonte-Nelson H.A.**, Picciotto M.R., Lukas R.J., Whiteaker P. (2021) Implications of oligomeric amyloid-beta (oA β 42) signaling through α 7 β 2-nicotinic acetylcholine receptors (nAChRs) on basal forebrain cholinergic neuronal intrinsic excitability and cognitive decline. *J Neurosci*, 41(3):555-575. doi: 10.1523/JNEUROSCI.0876-20.2020. PMID: 33239400; PMCID: PMC7821864.
 14. **Bimonte-Nelson H.A.**, +Bernaud V.E., +Koebele S.V. (2021) Menopause, hormone therapy and cognition: maximizing translation from preclinical research, *Climacteric*, 24:4, 373-381, DOI: 10.1080/13697137.2021.1917538.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Using isogenic hiPSCs to study the relationships between APOE isoforms, SARS-CoV-2 infection, endosomal dysfunction, and neural cell responses. David Brafman, PhD (PI). Arizona State University; Arizona Alzheimer's Consortium.

Specific Aims:

Specific Aim 1: Use hiPSC-derived 3-D cortical cultures to examine APOE isoform-dependent effects on receptor-mediated endocytosis. We hypothesize that APOE might influence levels of SARS-CoV-2 endocytosis through two non-mutually exclusive mechanisms: (i) Isoform specific differences in endocytic receptor expression and (ii) Isoform specific differences in receptor affinity. To test this hypothesis, we will measure the effects of APOE genotype on cell permissiveness to viral infection (**Sub-Aim 1.1**). In addition, we will measure the cell surface levels of endocytic receptors in isogenic cultures (**Sub-Aim 1.2**). Moreover, to functionally attribute any differences in levels of SARS-CoV-2 neurotropism to specific endocytic receptors we will disrupt their expression and function using genetic and pharmacological approaches (**Sub-Aim 1.3**).

Specific Aim 2: Determine the effect of APOE isoforms on endosomal trafficking and cell phenotypes in APOE isogenic neural cultures. In parallel with Aim 1, we will use biochemical, cellular, and genetic methods to test out hypothesis that APOE isoform-dependent differences result in basal levels of endosomal trafficking dysfunction (**Sub-Aim 2.1**). In turn, we will determine the extent to which this leads to APOE isoform-specific differences in cellular responses such as synaptic loss, inflammation, and cell death (**Sub-Aim 2.2**). In addition, we will determine if these cellular phenotypes can be mitigated by lowering basal levels of endosomal dysfunction (**Sub-Aim 2.3**).

Background and Significance:

Several genetic risk factors have been associated with increased susceptibility to SARS-CoV-2 infection and subsequent COVID-19 severity. Of these risk factors, polymorphism in the Apolipoprotein E (APOE) gene, a lipoprotein transporter involved in cholesterol metabolism, has been identified as one of the more prevalent. The role of these polymorphisms in human health have been mostly studied in the context of Alzheimer's disease (AD). As it relates to SARS-CoV-2, recent work has shown that patients homozygous for APOE4 showed an increased risk for severe COVID-19 independent of pre-existing comorbidities. However, the underlying mechanisms of how the presence of an APOE E4 allele increases risk of SARS-COV-2 infection and subsequent COVID-19 severity have yet to be elucidated. In addition, it is unclear if APOE4 modulates this risk through a loss-of-function or a gain-of-toxic-effects. Finally, it has not been investigated if APOE2 potentially exerts a protective effect against SARS-COV-2 infection susceptibility.

Although SARS-CoV-2 chiefly affects respiratory tissue, numerous studies have shown that infected patients present with neurological symptoms. In fact, analysis of brain tissue of COVID-19 patients has revealed the presence of viral RNA demonstrating viral infection of the central nervous system. Likewise, studies with animal and cell culture models have demonstrated that SARS-CoV-2 exhibits high levels of neurotropism. These studies have also shown that SARS-CoV-2 infection results in numerous neural cell responses including synaptic loss, release of inflammatory cytokines, and cell death. Finally, early research indicates that SARS-CoV might induce AD-related cellular and biochemical phenotypes such as elevated A β levels. However, the mechanisms by which SARS-CoV-2 induces these neural and AD-related phenotypes is unclear.

Preliminary Data, Experimental Design and Methods:

Generation of pure populations of functionally mature hiPSC-derived cortical neurons, astrocytes, and microglia. 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. These purified neuronal populations express robust levels of neuronal marker TUJ1 and mature neuron markers MAP2 and NEUN. On the other hand, astrocytes lack expression of neuronal markers and display immunoreactivity for the astrocytic makers S100 β and CD44. RNA-seq analysis of genes upregulated in the astrocytic population reveal high expression of astrocyte-specific markers (e.g., *CD44*, *VIM*, *LIF*). By comparison, the neuronal populations express high levels of neuronal-specific markers of largely cortical identity (e.g., *SLC17A6*, *GRIN1*, *GRIN2B*, *GRIN2D*). Importantly, RNA-seq analysis reveals a high degree of transcriptional similarity between cells isolated generated from independent differentiation demonstrating the reproducibility of our methods. Consistent with functional characteristics of neurons and astrocytes, we find that astrocytes exhibited slow calcium transients with longer periods compared to the rapid, frequent firing of neurons, further confirming cellular identity. Importantly as it relates to this proposal, we have confirmed that these astrocytes secrete robust levels of APOE and CLU. In addition, we have adapted previously published protocols to generate functional microglia-like cells from hiPSCs. 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 A β 42 as measured by real-time fluorescent microscopy.

Rapid and highly efficient generation of isogenic hiPSC lines. Using human induced pluripotent stem cells (hiPSCs) to investigate the mechanisms by which Apolipoprotein E (APOE) modulates Alzheimer's disease (AD) risk. We have previously used our highly efficient gene editing technologies to generate APOE isogenic and knockout (KO) hiPSC lines from a variety of non-demented control (NDC) and AD patients. In recent work published with Dr. Guojun Bu's group as well as work by our group, we have used isogenic hiPSCs to investigate the mechanisms by which APOE4 and APOE2 increase and decrease AD-risk, respectively. Briefly, with hiPSC-derived neural cultures we demonstrated that isogenic conversion of APOE4 to APOE3 reduced AD-related phenotypes including elevating levels of A β and phosphorylated tau and inducing synaptic loss. By comparison, analysis of mixed cultures derived from isogenic lines revealed that conversion of APOE3 to APOE2 decreased pathogenic amyloidogenic processing of APP as well as reduced A β release and levels of phosphorylated tau. Overall, these preliminary experiments demonstrate our ability to use isogenic hiPSC lines to investigate the mechanisms.

Experimental Designs and Methods

Specific Aim 1: APOE also employs receptor-mediated endocytosis for cell entry binding to the LDL receptor family including LDLR and LDL receptor protein 1 (LRP1), as well as cell surface heparan sulfate proteoglycans (HSPG). Notably, several enveloped RNA viruses have been shown to utilize these same LDLR receptors and HSPGs to facilitate their endocytosis⁴⁵⁻⁵¹. Indeed, recent work has shown that SARS-CoV-2 might interact with some these same receptors to facilitate endocytosis. Moreover, APOE has shown to display isoform-specific affinities to these various receptors and can form association with viral particles to influence endocytosis. As such, specific APOE isoforms might act in a gain-of-function manner to enhance viral endocytosis or in a loss-of-function manner by blocking viral binding to endocytic receptors. In addition, analysis of our neural cultures indicates APOE isoform-specific differences in the expression of these receptors that facilitate viral and APOE endocytosis. To that end, we hypothesize that APOE might influence levels SARS-CoV-2 endocytosis through two non-mutually exclusive mechanisms: (i) Isoform specific differences in endocytic receptor expression and (ii) Isoform

specific differences in receptor affinity. To test these hypotheses, cell surface as well as total expression levels of LDLR, LRP1, HSPG, and NRP1 will be measured in APOE isogenic cultures by gene expression analysis, flow cytometry, and Western blotting.

Specific Aim 2: Previous work has demonstrated impaired endosomal trafficking and other endocytic abnormalities, such as enlargement of early endosomes, in APOE4 neurons. To begin exploring some of these relationships, APOE isogenic cultures will be stained for Rab proteins and Rab effector proteins that specifically mark early (i.e., Rab5, EEA1), late (i.e., Rab7), and recycling (i.e., Rab11) endosomes. In turn, quantitative immunofluorescent imaging will be performed to quantify the number, size, and intensity of each of these endosomes. In addition, gene expression analysis and Western blot analysis will be performed to expression levels of various endocytic proteins. In addition, recent work has shown that levels of endogenous endosomal dysfunction, such as early endosomal enlargement, in AD hiPSC-derived neural cells are a direct consequence of APP β -CTF levels in a cell. In addition, reducing APP β -CTF levels through treatment with a β -secretase inhibitor reverses endosome dysfunction and associated cellular phenotypes. Notably, it has been suggested that APOE modulates intracellular β -CTF levels in an isoform-specific manner (i.e., E4>E3>E2). To determine the relationship between APOE isoforms and β -CTF levels, the levels of β -CTF in neural cultures will be measured by ELISA.

Proposed One-Year and Long-Term Outcomes:

This proposal seeks to use human-induced pluripotent stem cell (hiPSC)-based models to elucidate the relationship between APOE isoforms and SARS-CoV-2 risk. This research will significantly advance our understanding of the mechanisms that potentially modulate the short- and long-term neurological consequences of SARS-CoV-2 infection. Over the past year, we have developed the assays and begun to examine the impact of APOE isoforms on endosomal trafficking and dysfunction in AD. In the near future, we hope to examine these APOE-isoform dependent effects in the context of SARS-CoV-2 infection. In this vein, the preliminary data and models that will be generated as part of this proposal will allow us to apply for more comprehensive grants to funding agencies (e.g., NIH, Alzheimer's Association, American) to further mechanistically probe these links.

Year End Progress Summary:

As it relates to Aim 1, although it was initially speculated that SARS-CoV-2 enters cells the endocytic receptors ACE2 and TMPRSS2, recent work has shown that the expression of these receptors is absent in neural cells and entry into the CNS is likely facilitated through NRP1. Indeed, RNA-seq analysis of our neural cultures confirmed this finding. Moreover, analysis of our isogenic neural cultures revealed that the expression of NRP1 was significantly lower in APOE2 cultures compared to APOE3 cultures, suggesting that an APOE isoform-specific tropism might be facilitated through differences in expression levels of NRP1. In addition, analysis of our neural cultures indicates possible APOE isoform-specific differences in the expression of receptors (e.g., LDLR, LRP1) that facilitate viral and APOE endocytosis. With respect to Aim 2, RNA-seq analysis of isogenic cultures has shown that the expression of numerous genes associated with endosome formation (e.g. *RAB7A*), recycling and acidification (e.g. members of the vacuolar-ATPase proton pump), sorting (e.g. members of the Retromer complex), and trafficking (e.g. members of the Commander complex) are significantly downregulated in APOE2 neural cells. Thus, differences in basal levels of endosomal function might explain APOE-dependent effects as it relates to SARS-CoV-2 infection. Along similar lines, we have shown that in neural cultures isogenic conversion of APOE3 to APOE2 reduces β -CTF levels. Therefore, we hypothesize that endogenous β -CTF levels are correlated to a cell's resiliency to SARS-CoV-2-induced endosomal dysfunction in an APOE isoform-dependent manner.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Aging Effects and Sex Differences from E2 Exposure on Depression Phenotype. Cheryl D. Conrad, PhD (PI). Arizona State University; Arizona Alzheimer's Consortium.

Specific Aims:

To test the hypothesis that daily E2 exposure will block CORT-induced sex differences in depressive-like behavior and poor cognition via mTORC1 mechanisms during aging.

Background and Significance:

Depression is a complex mental disorder, affecting 264 million people worldwide and is characterized by altered mood and/or loss of interest in pleasurable activities. In the USA, depression is the highest ranked mental disorder for years lived with disability, a ranking that has remained unchanged from 1990 to 2013. Moreover, depression prevalence in women is nearly twice that observed in men and as individuals age, depression and anxiety become more common, with depressive symptoms being the largest predictor of disability in older adults. For middle-aged women, depression risk can be nearly six-fold higher following a history of depression, and two to three-fold higher even without a prior history. Studies show that in middle-aged women, mood improves following 17 β -estradiol (E2) treatment, although there are uncertainties. For example, in women who are in menopause, E2 treatment fails to improve mood and so combined with other research, these findings suggest that a sensitive window exists for estrogen-related efficacy. ***Consequently, the proposed studies investigated the middle-aged demographic pre-clinical model, representing a highly vulnerable period, using both females and males when depression risk is greatest, but also more likely to show benefits from intervention.***

Preliminary Data, Experimental Design and Methods:

Middle-aged (12 mo) male and female rats had their gonads removed (GDX) to eliminate their endogenous source of gonadal steroids and assigned a stress hormone treatment (CORT, 40 mg/kg, s.c. or vehicle, VEH) to produce a depressive-like phenotype. In addition, rats were subdivided into gonadal steroid treatment with estradiol (E2, 3.0 μ g or Oil, s.c.), which is a dose based upon effectiveness on improving cognitive performance in middle-aged GDX female rats. This led to a 2 x 2 x 2 design of Sex (Male, Female), Stress steroid treatment (CORT, Veh for CORT), and E2 treatment (E2, Oil vehicle for E2). After recovery from GDX (approximately 2 weeks), CORT/Veh and E2/Oil injections commenced for three weeks prior to the initiation of behavioral testing.

Behavioral testing occurred in the following order and with tasks that were successfully used to show significant outcomes following rodent treatment with CORT or E2 as it pertains to depressive-like behavior. CORT and E2 injections continued daily throughout behavioral testing procedures. Injections occurred at 7 AM and behavioral testing started at 9 AM and ended at least 1 hour before the light cycle transitioned.

1. (2 weeks): The radial arm water maze (RAWM) was used to assess working memory; a cognitive function impacted by depression and involves the prefrontal cortex brain region. RAWM requires rodents to swim to find hidden platforms and is challenging because it takes nearly two weeks to learn.
2. (2 days): The visible platform is used to determine that rats are capable of swimming and learning to escape. This task is relatively easy and helps interpret whether rats show motivation to swim and are capable of learning in a swimming task.

3. (10 days): Sucrose preference taps into depressive like behavior by assessing how much rats are willing to drink a highly palatable sugar solution over tap water. Rats that show anhedonia or reduced interest in pleasure will consume less sugar water than their counterparts. The variation of this task used takes ten days to complete.
4. (6 days): Social interaction tests whether rats will prefer spending time with conspecifics, as depressive-like behavior reduces social interaction. Testing takes 1 hour per rat due to acclimation procedures, but with the number of rats, six days were set aside to complete testing of all rats.
5. (2 days): Marble bury taps into active anxiety behavior, which is highly comorbidly expressed with depression, by assessing how rats interact with novel objects in their cage. Rats that are highly anxious will spend more time burying marbles and showing freezing behavior when not actively burying marbles. Testing takes 1 hour but we can test 8 rats at once and so this can be completed within two days.
6. (1 day): The elevated plus maze uses height to assess passive anxiety-like behavior. Rats that are highly anxious will avoid the arms that are open and allow one to peer below compared to the arms that are enclosed with tall walls.

Euthanasia occurred a few days following the end of the last behavioral task, reflecting approximately two months of CORT or E2 treatment. Serum was collected and will be assayed for steroid hormone levels and feedback hormone levels including LH and FSH. The brains were collected and will be processed by Dr. Huynh to evaluate mTORC1 protein levels using western blot and correlated with depressive-like profile.

Proposed One-Year and Long-Term Outcomes:

Rats will be ordered, and surgeries and behavior testing will be completed by the end of the one-year project period. We plan to 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 two years from study initiation, and a grant to study brain/behavior/aging/hormone relationships with depression in the middle-aged.

Year End Progress Summary:

The project timeline is shifted by 6 months because the funding was received at the end of the 2021 calendar year and so January 1, 2022, was essentially the start of the funding period. As such, the project is on schedule with the first half of the rats having completed behavioral testing and currently, the second (and last) half the rats currently being tested over the summer. Data analysis for behavior will be completed by September and brains will be assayed and completed by the end of the Fall semester in 2022. The goal is to write up all the data for a manuscript in the spring 2023 semester and submit a grant proposal during the summer.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Piloting an Evidence-based Family Caregiver Intervention via Video-conferencing. David W. Coon, PhD, Molly Maxfield, PhD, Dona Locke, PhD. Arizona State University; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

- a) Analyze structured interview and focus group data collected during the COVID 19 pandemic in 2020 from family caregivers of people with ADRD to refine CarePRO, an evidence-based family caregiver intervention for implementation via video conference platform (i.e., Zoom).
- b) Finalize a screening and interview protocol drawn from the NIH REACH trials and refined through the data collected in Specific Aim "a."
- c) After obtaining IRB approval, deliver the program (CarePRO Virtual) via video conference platform in a single-arm pre/post pilot feasibility and acceptability trial with 25 family caregivers affiliated with Mayo Clinic.
- d) Conduct appropriate mixed methods analyses to characterize the sample and evaluate the feasibility and acceptability of the trial.
- e) Disseminate findings through presentations at national conferences such as the Gerontological Society of America and the American Psychological Association.

Background and Significance:

Between now and 2025, Arizona is projected to have the greatest increase in its proportion of both people living with ADRD and their family or informal (family and friends) caregivers (Alzheimer Association, 2020). Family caregiving for people with dementia leads to a host of negative outcomes including poorer emotional well-being and new or exacerbated physical health problems as well as lowered income and financial health (see Alzheimer's Association 2020 for a review). These negative outcomes increase the of caregiver need for and use of health and social services (Kasper et al., 2015; Stall et al., 2019). When the normal daily routine of older adults who need the help of a caregiver is disrupted, adjusting to the new routine can be difficult. During unusual circumstances—such as pandemics or other situations that limit otherwise normal daily routines—caregiver outcomes are likely to be impacted further and new, innovative models of intervention needed. The COVID pandemic provided a unique opportunity to investigate the impact and identify opportunities for intervention to help family caregivers by adapting existing evidence-based intervention programs (e.g., CarePRO; Coon et al., 2012) for delivery through video-conferencing platforms such as Zoom.

Preliminary Data, Experimental Design, and Methods:

This project was built from focus group (N=24) and structured interview data (N=31) collected from family caregivers of people living with ADRD in 2020 during the COVID pandemic. Data were collected via telephone assessment and Zoom-based focus groups. The pandemic's impact on caregivers and participant feedback suggested our team quickly revamp evidence programs (e.g., CarePRO; Coon et al., 2012) for Zoom-based delivery and evaluation. The program has been adapted for this video-conference delivery and is named CarePRO Virtual.

In this project, we planned to recruit and enroll up to 20 Mayo Clinic Arizona family caregivers of individuals with ADRD into an evidence-based family caregiver intervention (CarePRO Virtual) delivered via video conferencing (i.e., Zoom). CarePRO Virtual is a 5 five-week group-based and individualized telephone coach call intervention designed to improve mood, coping skills, caregiver self-efficacy, and other quality of life outcomes. Each group consists of approximately

6 to 10 caregivers co-led by trained staff. Group meetings introduce skills (e.g., behavioral management, assertive communication, cognitive restructuring, stress management) and foster participant interaction and the individualized coach calls help tailor the skills to meet the needs and situations of the particular caregiver. The project also asks caregivers to participate in a 3-wave assessment of their caregiving experience including their basic demographic information, their mood, stress, coping strategies, and other quality of life indicators. Assessments will be conducted at baseline (pre-intervention or T1), immediately post intervention (approximately 9 weeks after baseline or T2). Dr. Coon and his staff who have experience in the delivery of CarePRO will use an NIH REACH trial train-the-trainer model (Belle et al., 2006) to implement the intervention with Dr. Locke and a member of her team as co-leaders.

Proposed One-Year and Long-Term Outcomes:

The proposed short-term outcomes are described in the Design and Methods section focusing on changes in mood, stress, efficacy and other quality of life indicators measured before and after involvement in the intervention. Data analyses from this mixed methods project would yield (a) professional presentations at meetings such as the Gerontological Society of America, the American Society on Aging, and/or the American Psychological Association and (b) manuscripts submitted to *The Gerontologist*, *Aging & Mental Health*, *Alzheimer's & Dementia*, *the Clinical Gerontologist*, and/or *Dementia*. Subsequently, the PIs will submit grants for future trials at NIA, US ACL, RRF Foundation or other sponsors based on these initial findings.

Year End Progress Summary:

The project completed Specific Aims (a), (b), and (c) refining the intervention and screening and interview protocols, as well as obtaining IRB approval. With regards to Aims (d) and (e) seventeen caregivers participated in the CarePRO Virtual intervention and completed all group sessions and telephone coach calls suggesting strong acceptability and feasibility. In terms of demographics, participating caregivers were all spouses with the vast majority self-identifying as non-Hispanic White (88.2%), college graduates or and those with advanced degrees (82.4%), not currently working outside the home (94.1%), and living in an urban or suburban setting (88.2%). Although analyses are still underway related to Aims (d) and (e), the proportion of caregivers reporting strong perceptions of benefit from participating in CarePRO was high including perceptions related to: overall benefit (100% of participants); better understanding of memory loss (100%); enhanced ability to care for their loved one (100%); that helped keep their loved one living at home (75%). The majority of participants also reported improvements in: bother associated with their loved one's behavioral changes (75%); their own overall confidence in care provision (83.4%); their level of preparation to provide care in the future (83.4%); and their communication with their loved one (75%). Participants saw more modest improvements in: their own mood or emotional well-being (58.3%); the amount of support they received from others (33.3%); and improvements in their loved one's mood or emotional well-being (50%). An important finding regarding feasibility is that a greater proportion of participants failed to complete the online post-assessment survey offered in this study when compared to completion rates in other intervention projects in our lab that conduct interviews via phone or zoom (29% vs. 15%).

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

The Effect of Amyloid on the Alzheimer's Intestinal Flora, a Combinatory Meta-Analysis.
Diego Mastroeni, PhD, Rosa Krajmalnik-Brown, PhD, Qiwen Cheng, PhD. Arizona State University; Arizona Alzheimer's Consortium.

Specific Aims:

Specific Aim 1: Evaluate available data on microbial community composition and function in fecal samples from human Alzheimer's Disease (AD) patients (meta-analysis) and compare these results to those from microbes present in intestinal tissue of AD patients to determine if tissue samples provide more information of the local microenvironment not afforded by human fecal samples.

1A) Isolate DNA from the transverse colon tissues from 25 controls [Braak 0-II/CRAD 0 (none)] and 25 Braak VI/CRAD C (abundant) AD cases and perform high throughput 16S rRNA gene amplicon sequencing to determine microbial composition. Predict microbial genomes and pathways using Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUSt2).

1B) Perform meta-analysis on existing human AD fecal 16S rRNA gene amplicon data to assess the strength of the present data, and to determine if fecal sample microbial communities are a true representation of the intestinal flora identified in *vivo* (Aim 1A). If they are not, determine the major similarities and differences in microbial composition and pathways.

Specific Aim 2: Evaluate the Amyloid Precursor Protein Pathway in human AD transverse colon.

2A) Measure A β gut concentrations and ratios (e.g., sAPP, APP, A β 40, A β 42, oligomeric A β and processing enzymes (BACE1, Secretases, PSEN1).

2B) Using the data from Aims 1A and 2A we will focus on possible links between gut tissue microbiota and APP processing. This will allow us to test whether the abundance of a particular APP processing molecule or A β variant is potentially causing an enrichment or reduction of specific gut microbes and altering microbial pathways.

Background and Significance:

Gut microbiota can influence physiological aspects of the human body, including the direct communication to the brain by way of neurotransmitter synthesis (Strandwitz P, 2018). The gut has approximately 500 million nerve cells that regulate a host of brain processes (Mayer EA, 2011). By now, the idea that gut microbiota affects a person's health is not revolutionary. It is known that these microbes influence a multitude of cellular processes and neurological conditions, like anxiety (Reid G, 2019), Parkinson's (Scheperjans F et al., 2015), and autism spectrum disorders (Krajmalnik-Brown R et al., 2015). Scientists have known for some time that gut microbiota plays a critical role in the production and biodegradation of neurotransmitters such as acetylcholine (ACh) (Strandwitz P, 2018), a critical co-factor in AD. This relationship between microbes and human health from an evolutionary perspective is unquestionable, but factors that can alter this symbiotic relationship between the host and microbes remain to be uncovered. One possible way is through the host defense mechanism. The host can interact with and regulate microbial-host interactions. For example, recent evidence indicates a role of amyloid beta (A β) as an antimicrobial peptide (AMP), a class of innate immune defense molecules that utilizes fibrillation to target many non-specific microbes, some infectious and some probiotic (Crunkhorn S, 2016). We have known for some time (the 1990s) that A β distribution spans much further than the brain. Work from Cabal et al. shows A β localization from the esophagus to the rectum in

humans(Cabal A et al., 1995). **Knowledge gap:** The fact that AD is associated with a hundred-fold increase in brain A β , and brain A β is cleared through the periphery(Marques MA et al., 2009), mandates the need to better understand the concentration of antimicrobial peptides (e.g., A β) that can potentially disturb the “normal” gut symbiosis and signaling between the host and microbes. Continued research into the diverse but related processes linked to AD risk is necessary for the successful development of alternative therapies not currently considered. **Goal:** The purpose of this application is to analyze the gut in AD patients and matched controls to determine: **1)** A β levels in AD gut (e.g., A β 42-A β 40 ratios) **2)** if A β levels/ratios are correlated with an enrichment/reduction of specific gut microbes and **3)** if findings of 1 and 2 correlate with existing literature on microbial communities in feces from AD patients. The **overarching hypothesis** is that gut A β levels modify intestinal flora composition, diversity, and metabolic pathways.

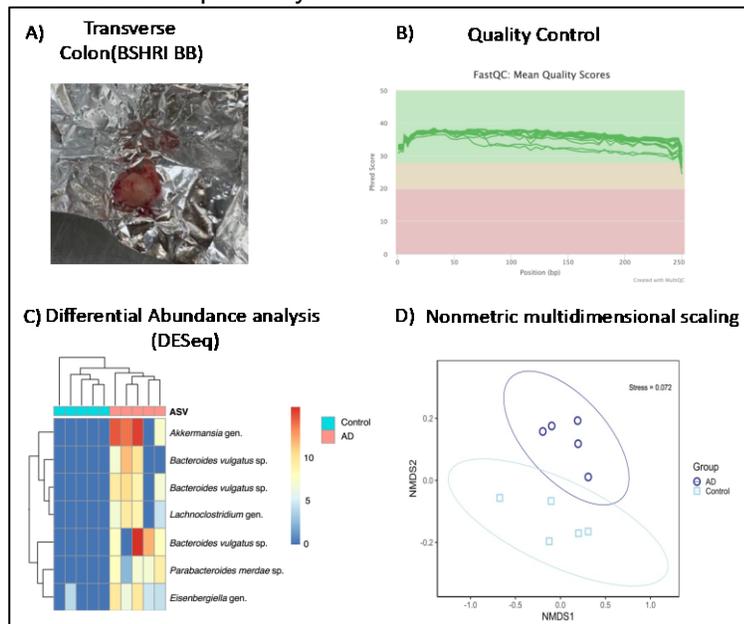


Fig. 1: The transverse colon (A) contains the highest microbial density recorded with up to 1012 microbes per gram of intestinal content. All samples from the brain bank passed quality control checkpoints (B) and were suitable for microbiome analysis, showing significantly higher abundances in AD gut tissue (C). Nonmetric multidimensional scaling plot illustrates the dissimilarity between AD and control samples based on the Bray–Curtis distance (D).

performed a western blot using an antibody to 6e10 (aa 1-16) in one AD case run in duplicate (**Fig. 2**). An interesting finding in the gut was the absence of amyloid monomers which is typically seen with 6e10 in brain and CSF(Grant MKO et al., 2019) at ~ 4kDa. This may indicate an increase in toxic amyloid aggregates in the AD gut, but more samples will be needed to confirm this hypothesis.

Experimental Design and Methods:

Samples: For this study, we will only use tissue from subjects where both the neuropathologist and anatomical pathologists have examined tissue samples from every organ and found no infection or inflammation. We will specifically omit individuals with a clinical diagnosis of Crohn’s, IBS, or any other gut-associated disorder. We will select only subjects with a mean RIN value of 8.5 or greater and PMI < 2.5 hours. For the sake of the agonal state associated with disease

Preliminary Data:

C.1. Distinctive gut microbes are associated with Alzheimer’s disease.

We analyzed the microbial communities present on the transverse colon tissues of five AD patients and five controls from Banner Sun Health Brain Bank. Our preliminary results indicate that microbial communities on gut tissue of AD patients were significantly different from those in controls ($p = 0.008$) (**Fig. 1D**). Species belonging to several genera, such as *Akkermansia* and *Bacteroides*, had significantly higher differential abundances in AD patients compared with controls (**Fig. 1C**), which is in line with literature(Haran JP et al., 2019;Zhang L et al., 2017).

C.2. Variants of A β are present in human AD transverse colon.

To determine if APP and A β variants are present in the AD colon we

duration, we will select subjects who have presented clinical symptoms of Alzheimer's disease for less than 5 years.

Aim 1A) Gut microbial community sequencing and analysis (Dr. Krajmalnik-Brown and Dr. Cheng):

To add power to our preliminary data presented in **Fig. 1**, we will extract DNA from the transverse colon of 25 clinically and pathologically confirmed AD cases and 25 matched controls (e.g., sex, PMI, ApoE status, age, etc.). We will perform 16S rRNA gene amplicon sequencing as previously described (Kang DW et al., 2017). We will analyze sequenced raw reads and explore microbial community composition using the Quantitative Insights into Microbial Ecology (QIIME 2, v2021.2) platform (Bolyen E et al., 2019). We will assess the gut microbial diversity using the R packages phyloseq (v1.34.0) (McMurdie PJ and Holmes S, 2013) and vegan (v2.5-7) (Jari Oksanen FGB, Michael Friendly, Roeland Kindt, et al., November 28, 2020). We will use the Linear discriminant analysis Effect Size (LEfSe, v1.0) (Segata N et al., 2011) and R package DESeq2 (v1.30.1) (Love MI et al., 2014) to identify microbes that are significantly different between AD patients and matching controls. We will predict microbial genomes and pathways based on 16S rRNA genes using PICRUSt2 (v2.4.1) (Douglas GM et al., 2020) and focus on possible links between microbial pathways and A β (Ilhan ZE et al., 2017).

Aim 1B) Meta-analysis of AD gut microbiota studies (Dr. Krajmalnik-Brown and Dr. Cheng):

We will search Google Scholar and Scopus for publications containing all the words "16S", "gut", "microbiota", "microbiome" and "Alzheimer's", and acquire the 16S rRNA gene sequences in these studies for the meta-analysis. We will also query two public databases, Sequence Read Archive (SRA) in NCBI and European Nucleotide Archive (ENA) using the keywords "Alzheimer's" and "microbiota" to download additional relevant data. We will process these data with QIIME 2, LEfSe, and R packages, and predict the microbial pathways with PICRUSt2 as described in Aim 1A. We will perform a distance-based redundancy analysis (db-RDA) using the R package vegan and build generalized linear mixed models (GLMMs) in the R package glmmTMB (Mollie E. Brooks KK, Koen J. van Benthem, Arni Magnusson, Casper W. Berg, Anders Nielsen, Hans J. Skaug, Martin Mächler and Benjamin M. Bolker 2017) to assess the influence of study-dependent factors, such as age, gender, and DNA extraction and sequencing protocols. In addition, we will incorporate the results from Aim 1A into the meta-analysis and measure similarities and dissimilarities between our work and other studies to evaluate if tissue samples provide extra information on gut microbiota that is not revealed by fecal samples. If important differences are found, we will use our microbiome knowledge to critically analyze possible reasons and implications of those differences.

Aim 2A) Measure A β concentrations and ratios [immunological studies (Dr. Mastroeni)]:

From the same 50 samples in Aim 1A we will perform western blots using the antibodies described in **Fig. 2**, and other APP processing molecules (e.g., PSEN1, alpha/beta/gamma secretases,

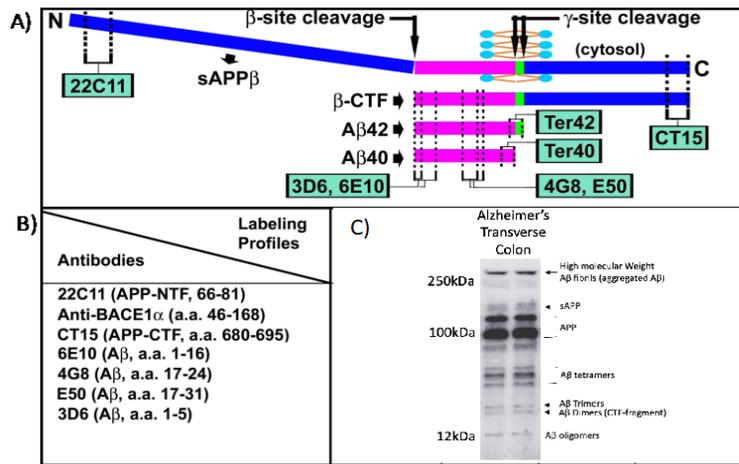


Fig.2: A) APP peptide and cleavage sites. B) Summary of the proposed antibodies to be used for differential peptide labeling by various antibodies targeting different epitopes on APP and its amyloidogenic proteolytic products. C) Western blot of an Alzheimer's transverse colon sample using 6E10 antibody. This shows the presences of amyloid in the colon.

BACE1). We will use the same published methods we routinely use, please see (Mastroeni D et al., 2013; Mastroeni D et al., 2015; Mastroeni D et al., 2010; Mastroeni D et al., 2017) for details.

Aim 2B) Identify possible links between microbial pathways and APP processing (Dr. Mastroeni, Dr. Krajmalnik-Brown, and Dr. Cheng): We will apply db-RDA and GLMMs, as described in Aim 1B, to determine the correlations between gut tissue microbiota (composition and pathways) and immunological parameters of interest (e.g., A β concentrations and ratios). This assessment is important for future research design and possible biomarker development.

Proposed One-Year and Long-Term Outcomes:

Our one-year goal is to generate competitive preliminary data for a larger application (i.e., R01). Our long-term goal is to start to focus our research on other organs besides the brain to give us clues on how Alzheimer's disease may start, many years from its clinical presentation.

Year End Progress Summary:

First and foremost, we would like to thank the Arizona Alzheimer's Consortium for funding our research. We have generated the kind of data necessary to apply for an NIH application and high-powered publications.

Human Gut Microbiome: Given this rather small niche, most of the data identified are novel, and we now can compare our data to existing genomic data extracted from feces. This is an ongoing study, and results from this study are to come in the coming months. We have made substantial progress on our proposed study as a whole. We have completed all the experimental procedures requiring human subjects and fulfilled all the proteomic and genomic studies. We are currently in the process of aligning all the unique microbes to proteomic databases to identify the unique taxa and peptides identified in the Alzheimer's gut but not in control samples. On the genus side, we have already identified a group of microbes using genomic techniques that are significantly enriched in the Alzheimer's gut (e.g., *Fusobacterium*, *Bacteroides*). This data alone is novel and is currently being drafted up by the team for publication. In addition to our proposed studies, exciting novel data from fungal communities were identified in these same samples. Although not proposed in the application, Dr. Krajmalnik-Brown provided additional funds to sequence these communities. These data are now being processed and promise exciting new leads into an uncharted microbial community that appears to be disease specific.

Human Proteome: On the human proteomics side, we have identified some very interesting biological pathways which are currently under investigation. We have identified several novel biological pathways that are downregulated in the Alzheimer's gut samples. One of the most significant downregulated biological pathways was the defense response to the bacterium. This novel finding is directly linked to the inability to clear potential threats and the inability to trigger a humoral response in the presence of noxious pathogens. Interestingly the most upregulated biological pathway in normal control is the antimicrobial humoral response (eleven up-regulated genes), or the ability to detect and mount an immune response to invading pathogens. The fact that greater than twenty proteins within the defense response to the bacterium pathway are downregulated in the AD gut indicates a failing complement system, or the inability to detect threats. As such, subsequent analysis showed a significant down-regulation of complement genes in AD gut compared to control ($p < .006$). Many of these same complement-related genes are dysregulated in the central nervous system too. The idea that diseases of the brain affect the entire system is not new, and this novel data is an extension of the systemic hypothesis.

Problems/Limitations: Some supply chain issues delayed some of the outsourced genomics, but we managed to generate all the data we proposed in the application in the allotted time.

Future goals: We have generated a wealth of information from humans to microbes. Our goal in the coming months is to generate a comprehensive manuscript focusing on the effect disease has on microbial communities and gut proteomics. We believe this data will be foundational in generating a testable hypothesis and applying for an NIH application.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Mobile phone accessibility of a motor-cognitive game within MindCrowd to increase participation among underrepresented minorities. Sydney Schaefer, PhD, Matthew Huentelman, PhD. Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aim(s):

The specific aim of this project is to develop a mobile phone version of our online motor-cognitive game, and to use MindCrowd to test how expanding its technological accessibility will increase participation among underrepresented minority groups.

Background and Significance:

Underrepresented minorities are not adequately recruited into Alzheimer's disease (AD) clinical trials even though they carry the greatest burden of the disease. For example, Blacks are 2x more likely to develop with AD than Whites, and Hispanics are 1.5x more likely than non-Hispanics¹⁻³; however, the median enrollment of non-Whites in an AD clinical trial is merely 6%⁴. To address this problem, the MindCrowd project was developed to engage large numbers of individuals in AD research via the internet that represent the U.S. both geographically and demographically. Thus far, MindCrowd has recruited over 200,000 individuals to participate as part of their electronic cohort. However, their ability to recruit among underrepresented minorities has historically been disproportionate to that of Whites, prompting new marketing efforts in 2020. Within the last year, MindCrowd has increased their recruitment among Blacks, Latinos, Asians, and mixed-race groups by over 200%. However, this issue of disproportionate representation among underrepresented minorities in AD research is not unique to MindCrowd. Other electronic cohorts such as the large WebAPT study also struggle with minority group representation, with over 92% of their cohort identifying as White⁵. A major limitation that prevents minority groups from participating may be the ways in which these electronic cohorts require their participants to engage, i.e., via a desktop computer. This is likely because web software that is compatible on a desktop is not always compatible with mobile or tablet devices.

The specific MindCrowd project we would like to make compatible on both desktop and mobile devices is Super G, an online video game that measures an individual's capability to learn a complex motor skill. Our 2020-2021 AAC funding supported the creation of Super G for an online platform, but it is currently only playable on a desktop or laptop computer. It requires participants to transport an astronaut (named Super G) between two planets using keyboard arrow presses. We are interested in this project for two reasons: first, we have shown that motor skill learning may be sensitive and specific to AD progression and pathology⁷⁻⁹, making it a potential strategy for clinical trial enrichment or monitoring disease progression in older adults. It is known that individuals with AD have preserved implicit learning capability compared to individuals with Parkinson's or Huntington's disease, even at advanced stages of the disease¹⁰⁻¹². Second, using a game as a point of participation in research offers a convenient, low-pressure, non-medicalized approach that appeals to a broad audience, thereby making it more inclusive for under-represented minorities who often express mistrust of medical professionals and methods^{1,2}. For example, a recent AARP survey has found that nearly half of older adult blacks and the majority of older adult Hispanics report enjoyment in playing online games, primarily on the phone, and identify as gamers.

Preliminary Data, Experimental Design and Methods:

We have preliminary data demonstrating that a decent percentage of individuals engages and completes the desktop only version of Super G. However, we know that roughly 26% of site visits

from unique visitors comes from mobile and tablet users. Thus, to maximize the total number of people who can have access to the game we need to develop a mobile compatible version of the game.

Participants and Experimental Design:

We will recruit approximately 400 participants to play either the desktop version of Super G or the newly implemented mobile version of Super G and compare how their performance varies dependent on device. We will collect race, ethnicity, age, and education data to observe the percentages of recruitment among each group and if there are any barriers for participation among each group that prevents them from completing the experiment fully.

Data Analysis:

To confirm that task performance is equivalent across devices, we will use a linear mixed effects models to determine the relationship of task performance on previously recorded cognitive scores, sex, age, and device type to determine if there are differences in task behavior dependent on device. If there is a significant difference in device type, we will look at how to adjust the game parameters between game versions that will help better align task performance along devices.

Additionally, a χ^2 test will determine if there are differences in registration rates by race and ethnicity. A significant difference will inform us if there is a significant difference in the proportion of registration among different race and ethnic groups.

Proposed One-Year and Long-Term Outcomes:

One-year outcomes include 2-3 manuscript submissions, an R21 submission to PAR-19-071 (under NOT-AG-20-053: “Sensory and Motor System Changes as Predictors of Preclinical Alzheimer’s Disease”) or PAR-20-150, and an AAC meeting presentation as well as at a national conference. Specifically, the focus of PAR-20-150 is on “*short-term exploratory or developmental research projects that have the potential to break new ground in the fields of minority health and/or health disparities or extend previous discoveries toward new directions or applications that can directly contribute to improving minority health and/or reducing health disparities in the U.S.*” Long-term outcomes include using Super G as a more inclusive enrichment strategy for AD clinical trial enrollment.

Year End Progress Summary:

1. Funding of postdoctoral fellowship through the National Institute on Aging (NIA). Preliminary data from the previous AAC application with Super G was recently used in a postdoctoral training grant for Dr. Hooyman through the NIA which was awarded as of 01/2022 (Grant # F32 AG071110-01A1). The purpose of this grant is to not only train Dr. Hooyman in the development cognitive-motor game software (Super G) but to also implement it within the MindCrowd cohort (Huentelman) for longitudinal study. A large portion of the grant argued that technology such as Super G provides greater engagement and accessibility than lab-based technology with a special emphasis on broadening the diversity among participants. This award will support Hooyman for 3 years as he and his sponsors (including Dr. Schaefer and Dr. Huentelman) work toward further development and integration of Super G and other motor-based assessments.

2. Full Implementation of the motor-cognitive game onto an online platform accessible both via desktop and mobile device. Our previous iteration of the motor-cognitive game was implemented online through a website, but it was only accessible to desktop users. With AAC funds, we have now converted the game to be desktop and mobile-device accessible. Previously, if a participant accessed the game from a mobile device, the underlying software would not render the game due to software compatibility issues. With the mobile-friendly version, the game fully renders and performs similar to any desktop device. This is an important development as our previous large-

scale testing observed that 26% of our web traffic was coming from mobile devices. As of the date of this report, 1,457 unique users have visited the Super G website with 385 coming from mobile devices. Through the desktop version we have had nearly 300 people play the game equating to a 28% hit rate of among all unique desktop users (i.e., the percentage of unique users that go on to play the game). If we assume the desktop numbers would carry over to our mobile unique users, we may expect an additional 28 new participants for every 100 new mobile users to access the Super G site. This level of productivity will push the level of engagement and scope to which we can conduct this type of research.

3. Validation of desktop to mobile device performance on Super G. After developing the online version of Super G through our AAC grant, we recently completed a large validation study through Amazon Mechanical Turk (mTurk) to observe what differences in Super G game play may occur between mobile and desktop users. The aim of this study was to determine what, if any, differences in game play may occur dependent on device type and if those observed differences interacted with other factors such as age or sex. Through mTurk we had 168 adults (mean age 38.9 years old) play the game via desktop and 111 adults (mean age 38.3 year of age) play the game via mobile. Each participant completed 75 trials of the task. Although we did observe that performance on mobile devices was different than that of desktop devices this appears to be only device dependent and we observed no interaction between age or sex with device that influenced the ability to play the game. This indicates that although performance may be difference between devices, which may be expected due to type of controller used, the type of device does not alter the relationship between age and sex with game performance, positioning us to now launch the mobile version in MindCrowd for a larger study.

4. Manuscript under peer-review. As we have continued to build out the Super G platform, we have also tested the validity of the online Super G game. This is a critical step to ensure that online, unsupervised performance is similar to that of in-lab, supervised performance. This manuscript is currently under re-review (a revise and resubmit) to the *Games for Health* journal. This study compared MindCrowd users who played the Super G online version with participants who played the Super G in-lab version. We note that we implemented a recruitment strategy to ensure that the MindCrowd group would be similar to that of the in-lab sample across age, sex, race and ethnicity. We found that the online MindCrowd cohort performed the game similar to the in-lab group, providing validation of the online version of Super G.

5. Presentation of research at two national conferences. We have presented our research findings at the American Society of Neurorehabilitation Annual Meeting, and at the North American Society for the Psychology of Sport and Physical Activity Annual Meeting. This work shows how performance on Super G is sensitive to APOE e4 carrier status. This work is ongoing with plans to submit a manuscript of these results to a peer-reviewed journal.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Selective Targeting of Toxic Tau Variants as a Therapeutic 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 P301L tau provides significant therapeutic benefit. To achieve this objective, we have devised the following specific aims:

Aim 1. We identified six nanobodies that selectively bind human AD based tau variants and block neuronal toxicity of the targeted variants. Here we will generate viral vectors to express each of the six nanobodies in an hiPSC cell line expressing the P301L mutation. The nanobodies will contain a peptide tag to facilitate transport in and out of neurons enabling intracellular targeting of neurons as previously demonstrated.

Aim 2. Identify the two most promising therapeutic tau nanobodies in an *in vitro* screen using the P310L hiPSC cell line. Each of the nanobodies will be separately expressed in the hiPSC cell line by viral infection. A viral 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. Substantial evidence indicates that pretangle oligomeric tau species rather than fibrillar forms are responsible for the neurodegenerative phenotype. Clinical therapeutic trials targeting either A β or tau have been largely disappointing resulting in many pharmaceutical companies leaving the neurodegenerative therapeutic field. However, a promising theory for the clinical failures to date is that toxic oligomeric protein variants need to be targeted instead of monomeric or fibrillar forms, and that these variants may need to be targeted intracellularly to restore neuronal health. **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:

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, A β , alpha-synuclein and TDP-43. We have extensive experience using the nanobodies to characterize ADRD tissue, CSF, and blood samples, and to demonstrate their potential diagnostic and therapeutic value for AD. We showed that the presence of specific oligomeric tau and A β 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. In addition to potential value as diagnostic reagents, the nanobodies also represent very promising therapeutics. We demonstrated that nanobodies can selectively target and clear toxic protein variants in both cell and animal models of neurodegenerative disease. We showed that selectively targeting oligomeric a-syn variants is more effective than targeting monomeric a-syn in an a-syn mouse model. Similarly, we showed that selectively targeting toxic oligomeric A β in a mouse model of AD is also a very promising therapeutic option. We found that targeting different toxic oligomeric A β variants in the AD mouse

model can have profoundly different therapeutic outcomes. **These results indicate that both the specific protein variant targeted and where it is targeted (intracellularly vs extracellularly) can make profound differences in therapeutic outcomes. This also provides a potential explanation for why current therapies against A β and tau have largely failed in clinical trials, since they have predominantly targeted either monomeric or fibrillar forms of A β or tau, and targeted them extracellularly rather than intracellularly where they may be able to restore homeostasis and rescue neuronal function.**

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 evaluate 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:

1. We verified that a peptide tag which we will add to the tau nanobodies enables the tagged nanobody to cross the blood brain barrier into the brain when administered systemically. We also verified that the peptide tag enables the nanobody to enter neurons in the brain and to clear the target antigen from the cells.
2. We utilized each of the six anti-tau nanobodies to probe post-mortem human AD brain tissue with varying Braak Stages (Braak stage I through VI). The goal was to identify tau variants that accumulate intracellularly in neurons in AD brain as a function of Braak stage. We identified three different nanobodies that selectively bind different tau variants that accumulate in neuronal cytoplasm during very early Braak stages, and other nanobodies that bind tau variants that accumulate in neuronal axons and glial cells during middle and late Braak stages. Interestingly a commercial antibody against phosphorylated tau only stained neuronal axons during late Braak stages, indicating that several of our anti-tau nanobodies selectively bind tau variants generated during early stages of AD. These tau variants are also present in neuronal cytoplasm and therefore represent very promising therapeutic agents to halt progression of AD during early stages of AD progression and potentially restore neuronal homeostasis.
3. We have identified a suitable mammalian expression vector for use in expressing our nanobodies in the tau cell models. We are currently subcloning each of the six tau nanobody genes into the mammalian expression vector.
4. We are in the process of obtaining a P301 induced human pluripotent stem cell line which we will utilize for the cell toxicity studies from Washington University. To obtain the P301 and isogenic control cell lines, we need to obtain the necessary Material Transfer Agreement. ASU and Washington University have just recently finalized the MTA, however the cell lines, while

generated at Washington University, are maintained at Cornell University, so we are now in the process of obtaining an MTA with Cornell University. Once the cells have finally been obtained, we will begin culturing the cells and transforming them to a cholinergic phenotype for the toxicity studies. Each of the six nanobodies will be transfected using a mammalian expression vector.

5. We will select the two most promising nanobodies from the in situ therapeutic assay for further in vivo animal studies. We expect that one or more of the three nanobodies that bind tau aggregates accumulating in neuronal cytoplasm during the very early stages of AD will be among the top two therapeutic candidates.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

The role of injury-induced necroptosis in contributing to Alzheimer's disease and neurodegenerative disorders. Sarah E. Stabenfeldt, PhD, G. Reed Bjorklund, PhD, David Brafman, PhD. Arizona State University; Arizona Alzheimer's Consortium.

Specific Aims:

Specific Aim 1: *Evaluate acute necroptosis following traumatic brain injury.* We will characterize necroptosis in adult mice within the first 48hrs following a focal brain injury (controlled cortical impact; CCI) using protein analysis (western blots and immunohistochemistry). The results from this study will provide unique insight into injury-induced necroptotic signaling on potentially priming the brain for neurodegenerative pathology.

Specific Aim 2: *Evaluate markers of chronic necroptosis and AD pathology following traumatic brain injury.* We will characterize evidence of necroptosis and hallmark AD pathology in adult mice at 1, 3, and 6 months following a focal brain injury (CCI) using protein (immunohistochemistry). The results from this study will provide unique insight into the continuum of injury-initiated necroptosis on AD pathology progression.

Background and Significance:

An increased risk for Alzheimer's disease (AD) and neurodegenerative disorders (NDDs) and following documented TBIs has been identified in the clinic ^{1,2} and AD-like pathology has been observed in preclinical TBI models ³⁻⁵. Many studies of military personnel have identified moderate to severe TBIs as an independent risk factor associated with an up to 60% increased risk of developing dementia ^{2,6}. Professional sports players involved in contact sports such as boxing, American football, and soccer are particularly vulnerable to developing NDDs due to head injuries ^{7,8}. A very recent special report by the Guardian, a British daily newspaper, documents a crisis of dementia among Rugby players. Findings from this report further state that concussion risks for women are greater than those for men and that concussion sufferers are twice as likely to develop brain diseases ⁹.

Commonalities exist between TBI and AD/NDDs pathologies including a dysfunctional blood-brain barrier ¹⁰⁻¹², neuroinflammation ¹³⁻¹⁶, protein dysregulation, and cell death via apoptosis and necroptosis. Yet, the direct connection and potential contribution of TBI to AD/NDDs pathologies remains elusive. Therefore, understanding and elucidating the potential role of TBI-induced neurodegeneration would afford an opportunity to detect, prevent, and intervene early. Here, we aim to characterize necroptosis and neurodegeneration following TBI in the mouse. Our analysis will focus on characterizing key aspects of the necroptosis (RIPK1, RIPK3, and MLKL signaling) and neurodegeneration (TDP-43, A β deposition, tau-phosphorylation).

Preliminary Data:

Using a well-established rodent TBI model (a unilateral controlled cortical impact; CCI)^{17,18} on a rodent with no genetic predisposition to neurodegenerative disease, we have recently discovered one of the defining pathologies associated with FTD and NDDs; TAR DNA-binding protein 43 (TDP-43) cytotoxicity. Hallmarks of TDP-43 cytotoxicity include TDP-43 translocation from the nucleus and aggregation in the cytosol, ubiquitination of the cytosolic TDP-43 aggregates, and hyperphosphorylation of TDP-43 ^{6,19}. Here, we propose performing long term analysis to track the progression, or resolution, of TDP-43 pathologies through late adulthood following a TBI incurred in early adulthood of our mouse model.

Experimental Designs and Methods:

For both Aims 1 and 2, we will use adult male mice with no genetic predisposition to neurodegenerative disease subjected to a unilateral CCI to the primary motor cortex. In Aim 1, levels of necroptosis will be evaluated at 6hr, 24hr, and 48hrs post-injury using western blots (tissue lysates) and immunohistochemistry (tissue sections) for necroptosis signaling molecules (RIPK1, RIPK3, and MLKL). For Aim 2, adult males at the time of TBI and will be sacrificed at 28-, 120- and 180-days post-injury. Uninjured control animals will be used for the three early time points together and additional uninjured control animals will be used for the 120- and 180-days post-injury timepoint to serve as age matched controls. Immunohistochemical analysis will be performed to determine the TDP-43 pathologies. 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. Immunofluorescent staining of both ipsi- and contralateral areas of the forebrain and cortex on TDP-43 pathologies. Quantitative comparisons will be made of all metrics and compared between group timepoints. For this analysis, manual cell counting for each of the listed TDP-43 pathologies will be performed by a blinded investigator using well matched tissue sections with defined areas of interest. Quantitative measurements will include normalization or grouping by lesion volume and location within individual animals as necessary and appropriate. 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. Results will be considered significant when the p -value is determined to be ≤ 0.05 and will be reported as mean \pm SEM.

Proposed One-Year and Long-Term Outcomes:

The results from this study will provide unique insight into the evolution of necroptosis following TBI and potential contribution to AD pathology. Data and findings from this proposal will be disseminated at the appropriate national conferences and journal publications. With prior support from AAC, the team of Drs. Stabenfeldt, Brafman, and recent addition of Dr. Bjorklund has submitted two NIH applications (one R03 and one R01) and one DOD proposal focused on the role of TBI in NDDs and AD in particular. Dr. Brafman and Dr. Stabenfeldt also have active funding from NIH R21 to develop a complementary in vitro study to probe the relation of injury-induced neuroinflammation and AD using hiPSCs. Coupling the in vitro and this proposed in vivo study will be very attractive for external funding agencies such as NIH, Alzheimer's Association, and American Federation for Aging Research.

Year End Progress Summary:

The progress in this year focused on two main research areas. First, we completed a series of immunohistological analyses in a preclinical mouse model of TBI to probe TDP-43 proteinopathies that emerge distal from a cortical injury (i.e., frontal cortex and spinal cord) out to 180 days post-injury. Our findings were recently presented at the National Neurotrauma Society meeting (June 26-29, 2022). The abstract from this presentation summarizes our key findings:

Directly following the primary impact from a traumatic brain injury (TBI), secondary injury sequelae ensues consisting of consecutive injury induced pathological processes. The primary injury event is considered irreversible, however, the secondary sequelae may be targeted to improve the patient's outcome in the minutes and years after suffering a TBI. In this histochemical based study, we have identified evidence of significant neurodegenerative effects in both the cortex distal from the initial injury region and the cervical spinal cord following a TBI. In both the cortex and cervical spinal cord of injured mice, we have revealed a significant number of neuronal cells that display a nuclear mislocalization of the TAR DNA Binding Protein 43 (TDP-43) when compared to age-

matched naïve control animals. Cells displaying this nuclear mislocalization also showed cytosolic accumulations of TDP-43 that appeared heavily ubiquitinated. These cellular abnormalities were detected post injury at up to 180 days. TDP-43 nuclear mislocalization, cytosolic aggregation with ubiquitination, and hyperphosphorylation, are known as hallmarks of amyotrophic lateral sclerosis (ALS) and are also found in ~50% of frontotemporal lobar degeneration, up to 70% of Alzheimer's disease patients, and is a prominent feature of Parkinson's and Huntington diseases. Our results indicate that secondary injury sequelae following a TBI leads to a chronic neurodegenerative state and supports a link between TBI and the development of neurodegenerative disease.

The second key area we focused on was to process and analyze RNAseq data from our preclinical TBI model from acute injury (24hr post-injury) to chronic injury (180 days post-injury). The samples were all collected and sent to a third-party vendor for processing and analysis. We are awaiting the final data set to be delivered (should be any day) and we will be able to run an exhaustive analysis on the emergence of neurodegenerative processes following TBI at the transcriptomic level. We look forward to combining these data with our IHC findings for a manuscript in preparation. Moreover, these data will serve the basis for a number of upcoming NIH (R21, F32, and R01) and DOD applications.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Empowering Structural MRI-Based Beta-Amyloid and Tau Burden Prediction with Federated Morphometry Feature Selection. Yalin Wang, PhD, Richard J. Caselli, MD, Kewei Chen, PhD. Arizona State University; Mayo Clinic; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Project Description:

In the A/T/N system - a recently proposed research framework for understanding the biology of Alzheimer's disease (AD) - the presence of abnormal levels of beta-amyloid ($A\beta$ as A in A/T/N) and tau (T in A/T/N) biomarkers is used to define the presence of biological AD. It would be highly advantageous to develop structural magnetic resonance imaging (sMRI) based $A\beta$ /tau pathology assessment system because of its wide availability and noninvasive nature. However, existing sMRI-based $A\beta$ prediction systems either suffers from low accuracy or does not produce biologically interpretable biomarkers. Our current project's **objective** is to build and deliver novel and efficient imaging algorithms that utilize sMRI to predict $A\beta$ and tau burden and enjoy excellent biological interpretability. **Hypothesis:** we hypothesize that our approach will maximize system statistical power of sMRI-based amyloid/tau prediction by enlarging sampling size without compromising data privacy, security, and regulatory constraints.

Specific Aim(s): To develop a novel privacy-preserving distributed machine learning approach, federated morphometry feature selection method, capable of efficiently extracting biologically interpretable morphological changes induced by $A\beta$ /tau burden and apply it to amyloid/MRI and tau/MRI brain scan pairs of three brain imaging cohorts.

- (a).** Develop new federated morphometry feature selection methods to extract $A\beta$ and tau burden induced morphometry changes;
- (b).** Validate the method by integrating them with our unique patch analysis-surface correntropy-induced sparse coding and max-pooling (PASCs-MP) to predict individual $A\beta$ /tau burdens with their cross-sectional sMRI data.

Background and Significance:

AD is the most common type of dementia. It is generally agreed that effective presymptomatic diagnosis and treatment of AD could have enormous public health benefits. Amyloid plaques, together with neurofibrillary tangles, are among the earliest signs of Alzheimer's disease (AD), appearing before any cognitive impairment and brain structure changes. Measuring beta-amyloid ($A\beta$) and tau burden at preclinical AD stages is believed to facilitate identifying individuals appropriate for a given intervention and improving the probability of therapeutic trial success. Brain $A\beta$ and tau pathology can be measured using positron emission tomography (PET) with amyloid and tau radiotracers directly in the brain, cerebrospinal fluid (CSF) measures or, more recently, blood-based biomarkers (BBBs) which are showing great promise. However, since current methods to detect $A\beta$ /tau burden are invasive (lumbar puncture for CSF), quite costly and not readily available (PET), and yet to have an established standard clinical practice (BBB), we still lack an economical and feasible alternative for the large-scale $A\beta$ and tau screening needed for AD prevention trials and routine clinical practice.

Structural magnetic resonance imaging (sMRI) is embedded regularly in routine clinical practice and preclinical research, including clinical trials for inclusion/exclusion criteria (e.g., to rule out other brain diseases) and/or as possible trial outcomes. Furthermore, it has been shown that $A\beta$ pathology correlates with sMRI-based atrophy measures in several structures, including total cortical and grey matter volumes, hippocampus, accumbens, thalamus, and putamen volumes. Patterns of tau pathology are mirrored by entorhinal thickness, hippocampal and ventricular

volumes. There is an emerging research interest in using sMRI biomarkers to assess and predict A β /tau pathology. Among these studies, regional or global brain structural volumes and cortical thickness are the commonly used sMRI measures. There is a dearth of studies to develop integrated shape analysis systems with strong statistical power to detect amyloid and tau burden for AD in asymptomatic individuals. Recently, we developed a shape analysis system to discriminate A β positivity in people with mild cognitive impairment (MCI) and cognitively unimpaired (CU) individuals and achieved promising results. Encouraged by our preliminary results, we propose here to develop novel federated learning algorithms to identify sMRI biomarkers that have the strongest prediction power on A β /tau burden and may be adopted for large-scale screening in AD prevention clinical trials and clinical practice.

Preliminary Data, Experimental Design and Methods:

Preliminary data We developed surface morphometry feature screening model with group lasso regression on the hippocampal surfaces. The shape is characterized through two different kinds of local measures, the radial distance and the surface area determined via tensor-based morphometry (TBM). The method is tested on 1,127 T1-weighted brain MRIs of AD, MCI, and CU, randomly assigned to five independent hypothetical institutions for testing purposes. We examine the association of MRI-based anatomical measures with general cognitive assessment, MMSE, to identify the morphometry changes related to AD deterioration. We discovered the regions irreverent to AD deterioration are concentrated at two hippocampal sub-regions, the subiculum and CA1, consistent with results from previous works.

Experimental design and methods We propose federated morphometry feature selection by federated group lasso regression with our surface TBM features. Group lasso is a prevalent technique for group-wise feature selection for high-dimensional data. In our formulation, each of the local institutions calculates its own gradient locally and uploads it to the master server. The latter is used to compute the global update gradient back to all the local institutes without data leaking. We will conduct comprehensive experiments to validate our research on Alzheimer's disease neuroimaging initiative (ADNI) cohort.

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 NIH R01 grant for an in-depth study to National Institute on Aging in 2022.

Year End Progress Summary:

Tetrahedral Spectral Feature-Based Bayesian Manifold Learning for Grey Matter Morphometry Our prior work demonstrated the usefulness of tetrahedral spectral features for grey matter morphometry. However, most of the current methods provide a large number of descriptive shape features, but lack an unsupervised scheme to automatically extract a concise set of features with clear biological interpretations and that also carries strong statistical power. We introduce a new tetrahedral spectral feature-based Bayesian manifold learning framework for effective statistical analysis of grey matter morphology and evaluate the proposed system on the ADNI cohort, using subjects' sMRI covering the range from CU to full-blown AD. Our analyses suggest that our work compares favorably with seven other baseline algorithms to obtain grey matter morphometry-based diagnoses. This work has been published in *Med Image Anal* (Impact factor = 11.148).

Predicting Brain Amyloid using Multivariate Morphometry Statistics, Sparse Coding, and Correntropy One of the presymptomatic AD hallmarks is the accumulation of A β plaques in the human brain. However, current methods to detect A β pathology are either invasive (lumbar puncture) or quite costly and not widely available (amyloid PET). Our prior studies show that hippocampal multivariate morphometry statistics (MMS) are an effective neurodegenerative

biomarker for preclinical AD. We attempt to use sMRI-based MMS to make inferences regarding brain A β burden at the individual subject level. We propose Patch Analysis-based Surface Correntropy-induced Sparse-coding and Max-Pooling (PASCs-MP) to reduce MMS feature dimensions and apply a binary random forest classifier to predict brain A β positivity. We test our method in two independent cohorts, 841 subjects from the ADNI and 260 subjects from the Open Access Series of Imaging Studies (OASIS). Our results are superior to state-of-the-art brain MRI measures. This work has been published in *Front Neurosci* (Impact factor = 4.677).

Federated Morphometry Feature Selection for Hippocampal Morphometry Associated Beta-amyloid and Tau Pathology One of the particular neurodegenerative regions is the hippocampus where the influence of A β /tau has been one of the research projects focuses on the AD pathophysiological progress. We propose Federated Morphometry Feature Selection (FMFS) model to examine subtle aspects of hippocampal morphometry that are associated with A β /tau burden in the brain, measured with PET. Experimental results on the ADNI dataset demonstrated that FMFS achieves an 89x speedup compared to other published state-of-the-art methods under five independent hypothetical institutions. In addition, the subiculum and cornu ammonis 1 (CA1 subfield) were identified as hippocampal subregions where atrophy is strongly associated with abnormal A β /tau. As potential biomarkers for A β /tau pathology, the features from the identified ROIs had greater power for predicting cognitive assessment and for survival analysis than five other imaging biomarkers. This work has been published in *Front Neurosci* (Impact factor = 4.677).

Studying APOE- ϵ 4 Allele Dose Effects with a Univariate Morphometry Biomarker A univariate neurodegeneration biomarker (UNB) based on MRI with strong statistical discrimination power would be highly desirable for studying hippocampal surface morphological changes associated with APOE ϵ 4 genetic risk for preclinic AD research. However, existing UNB work either fails to model large group variances or does not capture AD-induced changes. We proposed a subspace decomposition method capable of exploiting a UNB to represent the hippocampal morphological changes related to the APOE ϵ 4 dose effects among the longitudinal APOE ϵ 4 homozygotes (HM, N = 30), heterozygotes (HT, N = 49) and non-carriers (NC, N = 61) from the Arizona APOE cohort. The proposed UNB demonstrates a more substantial statistical discrimination power to distinguish the longitudinal groups with different APOE ϵ 4 genotypes than the hippocampal volume measurements. And different APOE ϵ 4 allele load affects the shrinkage rate of the hippocampus, i.e., HM genotype will cause the largest atrophy rate, followed by HT, and the smallest is NC. This work has been published in *J Alzheimers Dis* (Impact factor = 4.472).

Integrating Transcriptomics, Genomics, and Imaging in Alzheimer's Disease: A Federated Model Genome-wide association studies (GWAS), and transcriptomics—the study of gene expression—play an important role in understanding AD etiology and progression. Sophisticated imaging genetics systems have been developed to discover genetic factors that consistently affect brain function and structure. However, few methods have been developed to discover and infer multimodal relationships among sMRI, GWAS, and transcriptomics. We propose Genotype-Expression-Imaging Data Integration (GEIDI) model to identify genetic and transcriptomic influences on brain sMRI measures. Experimental results on the ADNI dataset demonstrated our proposed method outperformed state-of-the-art expression quantitative trait loci (eQTL) methods for detecting genetic and transcriptomic factors related to AD and has stable performance when data are integrated from multiple sites. This work has been published by *Front Radiology*.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 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 (PI), Heather Bimonte-Nelson, PhD (Co-I). 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 the menopausal transition. 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 transitional menopause. **This project corresponds with the sister project by PI Dr. Bimonte-Nelson. The research proposed here will support a new collaboration with Dr. Heather Bimonte-Nelson to study the molecular mechanisms underlying memory changes associated with the age-related menopausal transition and surgical reproductive tract manipulation, including hysterectomy. 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). Uniquely, female mammals (e.g., rats, mice, humans) go through significant 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 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 ovarian menopause status, including surgical menopause 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 propose to collaborate with Dr. Bimonte-Nelson in 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.**

Proposed One-Year and Long-Term Outcomes:

Rats were ordered, and surgeries and behavior testing were completed, and all tissue collection has been completed. RNA and DNA extraction and sequencing will be completed by the end of the one-year project period. We plan to analyze the DNA and RNA sequencing data

and write the data into manuscript form immediately after this time period. We will work with the Bimonte-Nelson lab to also incorporate behavioral cognitive data, correlating it with changes observed in the molecular data. Regarding long-term outcomes, expected deliverables include a manuscript submitted within two years from study initiation, and a grant to study brain/behavior/aging/hormone relationships with hysterectomy in collaboration with the Bimonte-Nelson lab. Regarding analyses of uterine and brain tissues, we will identify potential mechanistic information that could identify new relationships and drivers for changes observed in both the uterus and brain following ovarian modulation; such work will aid in characterizing these two critical structures across the trajectory of female aging. These outcomes will be the focus of a future collaborative NIH grant, which will take a systems approach to further understand reproductive health and brain function, with an eye toward the development of clinical therapeutics to optimize health outcomes for women across the lifespan.

Year End Progress Summary:

The Bimonte-Nelson lab ordered rats and performed surgeries and behavioral testing. We have completed tissue collection for molecular analysis and completed all extractions of RNA and DNA and sequencing. Our laboratory teams have had joint meetings and together, we have collected tissues from behaviorally tested animals. The tissues are being processed and analyzed by the Wilson lab team and will be correlated with behavioral outcomes measured by the Bimonte-Nelson lab. This is a truly cross-disciplinary and successful collaboration, including routine communication, before, during and after sample collection to ensure minimal batch effects and the most stable DNA and RNA collection possible. We are so thankful to the Arizona Alzheimer's Consortium for the resources to initiate this novel collaborative relationship. We are excited to see where the future data will lead us as we move forward.

We are working with the Bimonte-Nelson lab to write a manuscript based on the joint molecular and behavioral findings of this project funded this year by the AAC and anticipate submitting at least two manuscripts based on this work, acknowledging funding from the AAC: **+denotes graduate or postdoc student in lab; ^denotes undergraduate student in lab**

1. +Lizik, C., +Bernaud, V., Plaisier, S., **Wilson, M.A.**, Bimonte-Nelson, H.A. (in prep) Correlating molecular changes in the uterus with behavioral changes in a model of menopause.
2. Plaisier, S., +Lizik, C., +Bernaud, V., Bimonte-Nelson, H.A., **Wilson M.A.** (in prep) Uterus gene expression between left and right horns and correlation with ovary function.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Investigation of the structure and activity of Tau protein aggregate formation. Carol Huseby, PhD, Eranjalee Ranaweera, Po-Lin Chiu, PhD, Debra Hansen, PhD, Geidy Serrano, PhD, Paul D. Coleman, PhD, Jeffrey H. Kordower, PhD, Thomas Beach, PhD, Petra Fromme, PhD. Arizona State University; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Specific Aim(s)

- 1) Investigate the mechanism of tau aggregate formation in insect and human cell lines. We will establish insect and human cellular models overexpressing tau to observe tau aggregate formation in the cytosol.
- 2) Study the effects of AD tau polymorph seeding on cellular proteostasis. Structural comparisons of intracellular protein complexes will be made across treated cell culture, authentic human AD brain tissue, and healthy controls.
- 3) Examine combinatorial pattern of post-translational modifications leading to disease associated variants of tau aggregates. It has been hypothesized that posttranslational modification and especially phosphorylation plays a key role in the formation of tau isomorphs in the AD brain.

Background and Significance:

A hallmark of many neurodegenerative diseases is the presence of inclusions within neurons and/or glia that are comprised of fibrils formed from the microtubule-binding protein tau. Tau proteinopathies or tauopathies, are multi-factorial complex diseases in which brain cell mortality leads to memory loss and cognitive decline. Prevalence differs with associated risk factors and definitive diagnosis comes post-mortem after histochemical interrogation of brain tissue. Classical stages for neurodegenerative tauopathies can be clocked by distinct cellular and neuroanatomical distribution of the pathological tau inclusions. In many cases of AD, the initial accumulations of neurofibrillary pathology begin in locus coeruleus, entorhinal cortex, and hippocampus years before the onset of clinical symptoms such as progressive memory loss. With the recent medium resolution structure determination (2.3 – 3.4Å) of insoluble fibrils of tau protein in multiple diseases, we now see that the beta sheet core fold is disease specific. Interestingly, it was found that recombinant tau protein induced by heparin to aggregate in vitro forms multiple polymorphs unlike those extracted from human brain, highlighting the need for new model systems to explore aggregate polymorphs. Recent evidence supports cytoplasmic crowding and phase separation as influential, leading to droplets and aggregate formation for proteins with low complexity domains characterized by stretches of low amino acid variance resulting in polarity distribution along the peptide backbone. Additionally, an obvious interaction is that of post-translational modifications on intrinsically disordered tau protein. Hyper-phosphorylation or other post-translational modifications increase the polarity distribution along the intrinsically disordered tau molecule and may drive the hydrophobic regions of tau to condense and form hydrogen bonds between the most hydrophobic amino acid sidechains. These and other forces combined in the microenvironment of Tau protein within a cell can lead to a distinct aberrant conformational fold of the Tau protein.

Questions. What molecular mechanism or aspects of cellular environment drive the conformational variants of tau protein aggregates in a disease specific manner? Are these tau variants toxic? Are these tau variants or strains transmissible via seeding like that seen in prion disease?

Hypothesis. The environment of the cytosol influences tau variant conformation and these aberrant polymorphs are toxic to protein complexes and structures in neurons and glial cells. Answers to these questions can reveal the pathways of molecular dysregulation occurring in disease.

Experimental Designs and Methods:

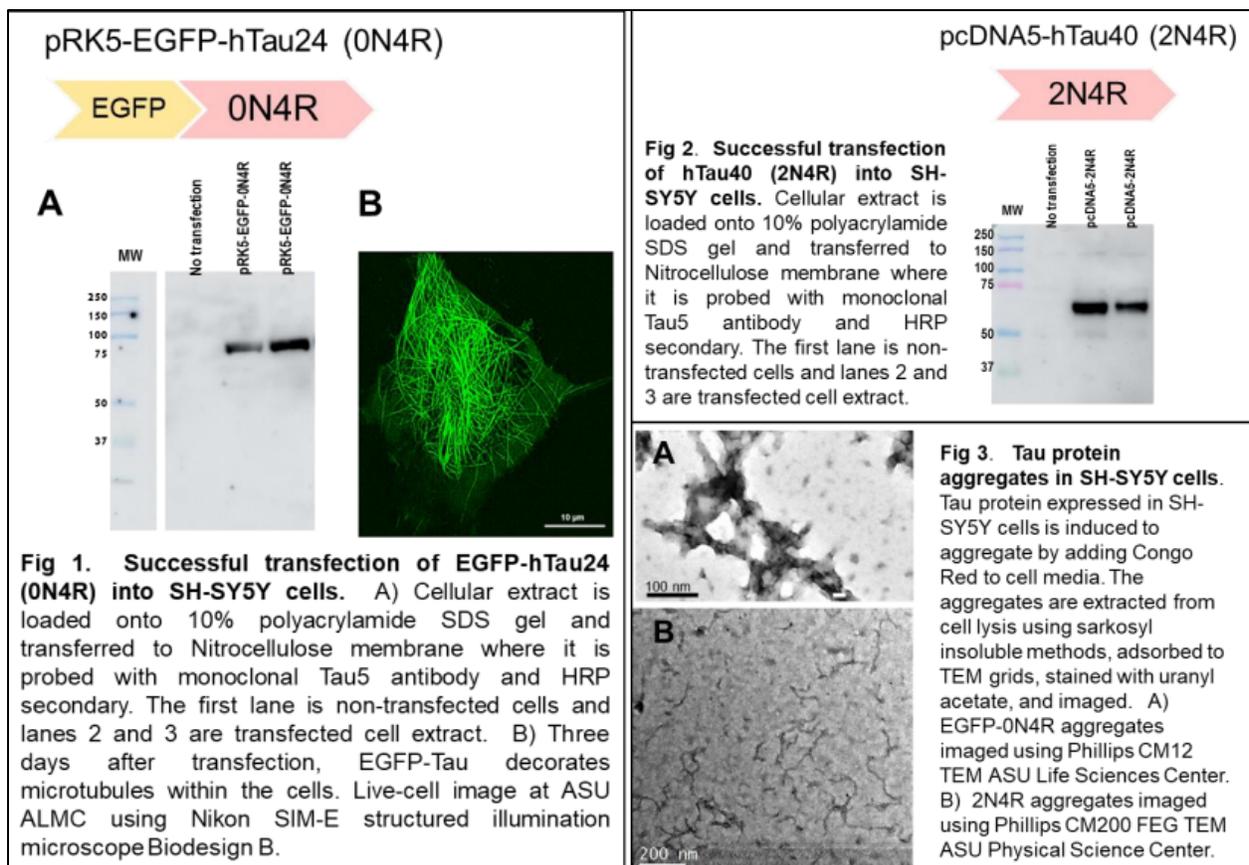
First, we propose to develop in vitro cellular systems of both insect and neuroblastoma human cell cultures expressing tau protein to investigate how the cytosolic and cellular environment influence the aggregate propensity and activity of tau protein using fluorescent microscopy and cryo-EM. We will look for aggregates and related protein aggregate structures such as the formation of ribosomal protein crystals and tau droplets and identify their location in the cellular cavity. Proteins expressed in insect cells can form crystals in living cells facilitating new methodological analyses. The structures of the tau aggregates will be studied by a combination of X-ray solution and (if tau nanocrystals are detected) crystallography studies with X-ray Free electron lasers combined with cryo-EM and tomography. Second, we will study the influence of abnormal tau protein conformations on the structure and/or density of protein complexes in our model cellular systems. In parallel, we will study protein complexes in authentic human brain tissue using structure determination approaches to search for differential structural manifestations in disease by a combination of electron microscopy (EM) and electron tomography. Cryo EM will allow us to look at the core structure of each Tau aggregate polymorph created after changes in the cytosol microenvironment around Tau protein expressed in our cellular models. Focused ion beam scanning electron microscopy (FIB/SEM) has been recently established at ASU and the basic setup of the cryo-FIB tomography became operational in the spring of 2022. Cryo-FIB will allow for visualization of tau aggregates and their cellular interaction partners in the tau cell culture models and the AD brain sample in vitreous ice in 400 nm lamellar sections of cells that are “milled out” from the cell by the focused ion beam.

Proposed Two-Year Outcomes:

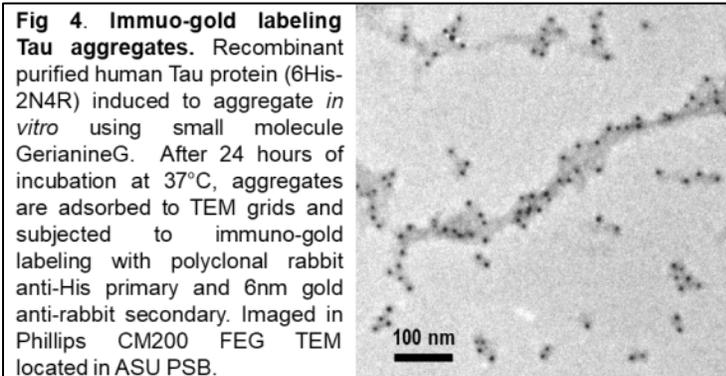
In the upcoming year, we will continue to refine our cryo workflow both for Tau aggregate polymorph core structure determination as well as Tau aggregate intracellular interactions using a variety of structural biology methods including SONNIC, for identification of potential Tau nanocrystals, as well as cryoEM, cryoFIB, cryoEM tomography, and X-ray free electron lasers for structure determination. Po-Lin Chiu, faculty in CASD at ASU, will support the team in the tomography reconstruction of intracellular environments. We are excited for the commissioning of two new instruments at ASU this summer. First, a new Leica EM ICE high-pressure freezer allowing cryo-tissue preparation of thicker samples for cryoFIB milling and second, a new cryoEM pre-screening instrument Talos L120C G2 cryo-ready transmission electron microscope (TEM), improving our cryo-EM workflow and adding additional capabilities to our research. With the new high-pressure freezer, we will be able to prepare small tissue slabs for slice-and-view serial imaging using cryoFIB at a resolution up to 10 nm each image while moving through brain tissue or cells. We will work closely with Thomas Beach and Geidy Serrano to access human brain tissue for cryoEM aggregate structural work and precise cryoFIB tomography studies. We anticipate this work will result in grant submissions, high-quality publications, and additional collaborations expanding the collaborations within the Arizona Alzheimer's Consortium network and further expanding the network by external collaborations.

Year 1 Progress Summary

Specific Aim 1: Establish Cellular models for the study of tau aggregate formation. Our team has successfully expressed the human tau protein isoforms within both mammalian and insect cells. The genes for the native Tau isoforms have been cloned into mammalian and insect plasmids for transfection protocols. After the initial testing of expression, mainly focusing on the longest and the shortest Tau-isoforms in both the mammalian and insect cell systems, we have designed full Tau isoform sets of plasmids for mammalian cell expression (3 sets) and insect cell expression (2 sets) that we will receive in June 2022. Each set includes all six isoforms of human brain Tau protein. The nomenclature of the isoforms is described by XNxR, with (X= 0,1 or 2) describing the number of N terminal repeats and (x= 3 or 4) giving the number of microtubule binding repeats. (For mammalian plasmids: **set 1** pcDNA5-2N4R, pcDNA5-1N4R, pcDNA5-0N4R, pcDNA5-2N3R, pcDNA5-1N3R, pcDNA5-0N3R (**set 2** includes N-term His tag, **set 3** includes N-term EGFP tag) and for insect cells: **set 1** pLEX-DC-2N4R, pLEX-DC-1N4R, pLEX-DC-0N4R, pLEX-DC-2N3R, pLEX-DC-1N3R, pLEX DC-0N3R (**set 2** includes N-term His tag)).



Using SH-SY5Y human neuroblastoma cells, a fluorescent tagged Tau human brain protein isoform was expressed at high levels after transfection with mammalian plasmid pRK5-EGFP-0N4R (Fig 1A). We used live-cell imaging by super-resolution microscopy and the exciting results show that the EGFP-Tau is rapidly expressed in cells and quickly binds and decorates the microtubules (Fig 1B). A second mammalian plasmid was tested (pcDNA5-hTau40 (2N4R)) containing an insert of the untagged longest isoform of human brain Tau. This Tau form was also expressed at high levels in SH-SY5Y neuroblastoma cells (Fig 2). To test for a cellular environment permissive to Tau aggregation after over-expression, we used a small molecule Tau

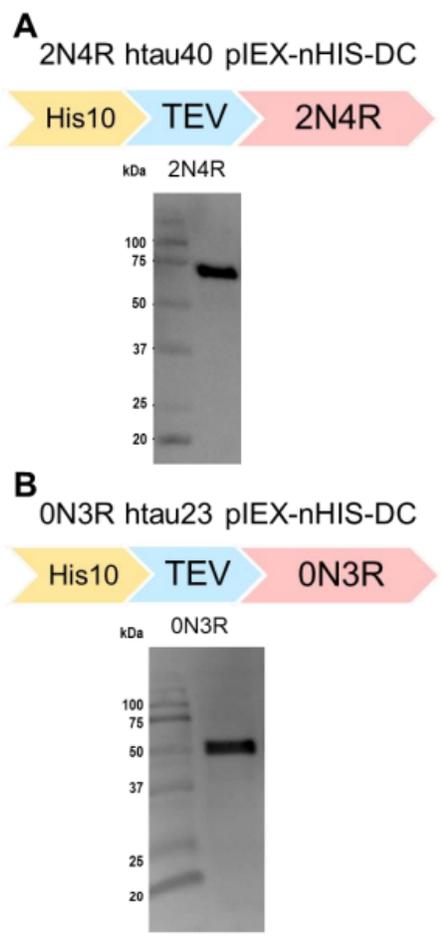


protein aggregation inducer (Congo Red) at 10 μ M in the cellular media for seven days after transfection. The inducer was refreshed each time the culture media was changed. The Tau protein aggregates are extracted by sarkosyl separation methods including a series of high and low centrifugation steps. We were very excited to find evidence of Tau aggregates within the cells in the cellular extract imaged by negative stain TEM (Fig 3AB). In year 2 we will further investigate the aggregate formation in the cell extract by TEM, where we study the full set of six mammalian pcDNA5-Tau plasmids each containing a different human Tau brain isoform both with and without the N-terminal tag of six Histidine (6His-2N4R, 6His 2N3R, 6His-1N4R, 6His-1N3R, 6His-0N4R, and 6His-0N3R). This tag will give us a clear immuno-label validation after expression and aggregation induction in cells like that shown for recombinant Tau aggregate structures immuno-gold labeled with 6nm gold nanoparticles and imaged negative stain in TEM (Fig 4). We are also growing mammalian Tau transfected cells on TEM grids for intracellular interaction structural studies (See Specific Aim 2).

Spodoptera frugiperda Sf9 cells are derived from the immature ovaries of fall armyworm moth pupae. Sf9 cells are a widely used insect cell line for eukaryotic protein expression having advantages of high expression of human protein, easy manipulation, and posttranslational modification landscape similar to mammalian cells. We have successfully infected Sf9 cells in culture with genes for the longest and shortest His-tagged human Tau isoforms (10His-2N4R and 10His-0N3R (Fig 5AB)). We will now test the cellular environment for permissive aggregation with the small molecule Tau aggregate inducer Congo Red. Sf9 cells expressing Tau are grown on TEM grids for intracellular interaction studies (see Specific Aim 2).

In order to measure the outcome of changes we will be making in the microenvironment of the transfected cellular models and the subsequent effect on the Tau aggregates, we are developing

Fig 5. Successful expression of human Tau isoforms in Sf9 cells. Tau isoform gene is shuttled into Sf9 cells using a baculovirus expression system. A) Cellular extract from cells infected with 10His-hTau40 (2N4R) is loaded onto 10% polyacrylamide SDS gel and transferred to Nitrocellulose membrane where it is probed with monoclonal anti-His antibody and HRP secondary. B) Cellular extract from cells infected with 10His-hTau23 (0N3R) is loaded onto 10% polyacrylamide SDS gel and transferred to Nitrocellulose membrane where it is probed with monoclonal anti-His antibody and HRP secondary.



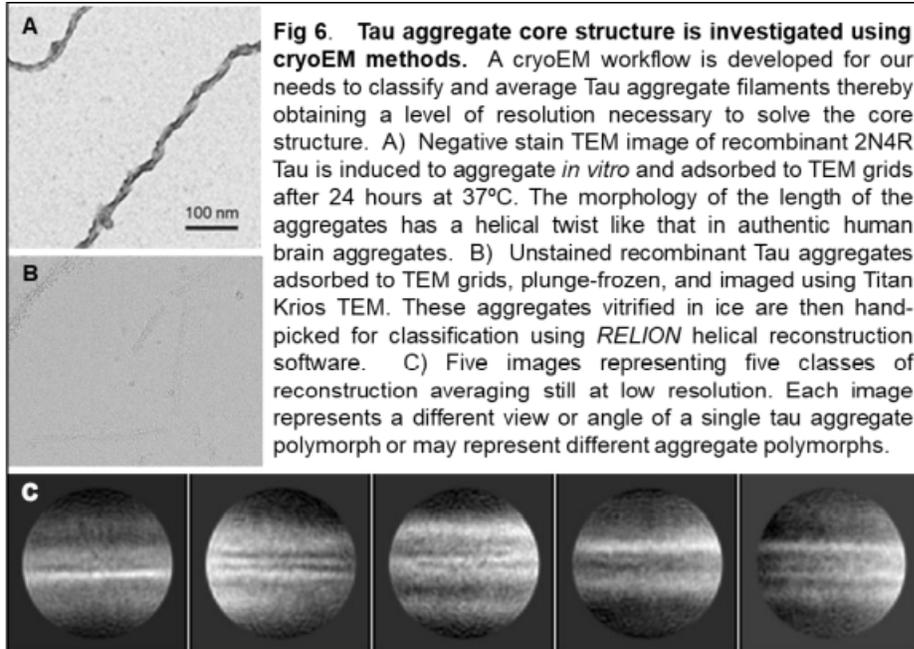


Fig 6. Tau aggregate core structure is investigated using cryoEM methods. A cryoEM workflow is developed for our needs to classify and average Tau aggregate filaments thereby obtaining a level of resolution necessary to solve the core structure. A) Negative stain TEM image of recombinant 2N4R Tau is induced to aggregate *in vitro* and adsorbed to TEM grids after 24 hours at 37°C. The morphology of the length of the aggregates has a helical twist like that in authentic human brain aggregates. B) Unstained recombinant Tau aggregates adsorbed to TEM grids, plunge-frozen, and imaged using Titan Krios TEM. These aggregates vitrified in ice are then hand-picked for classification using *RELION* helical reconstruction software. C) Five images representing five classes of reconstruction averaging still at low resolution. Each image represents a different view or angle of a single tau aggregate polymorph or may represent different aggregate polymorphs.

our cryoEM workflow to solve Tau aggregate core structures. Using cryoEM images of recombinant Tau aggregates adsorbed to TEM grids plunge-frozen in liquid ethane, we have succeeded in obtaining low-resolution structures of Tau aggregate polymorphs. The reconstruction process requires thousands of images from which we will

pick, classify, and average many fibril particles together to obtain a high-resolution structure of aggregate polymorphs and ultimately the cross-sectional solution of the core. We will continue to collect additional data and refine our reconstruction protocol to reach the highest-resolution possible. (Fig 6A-C).

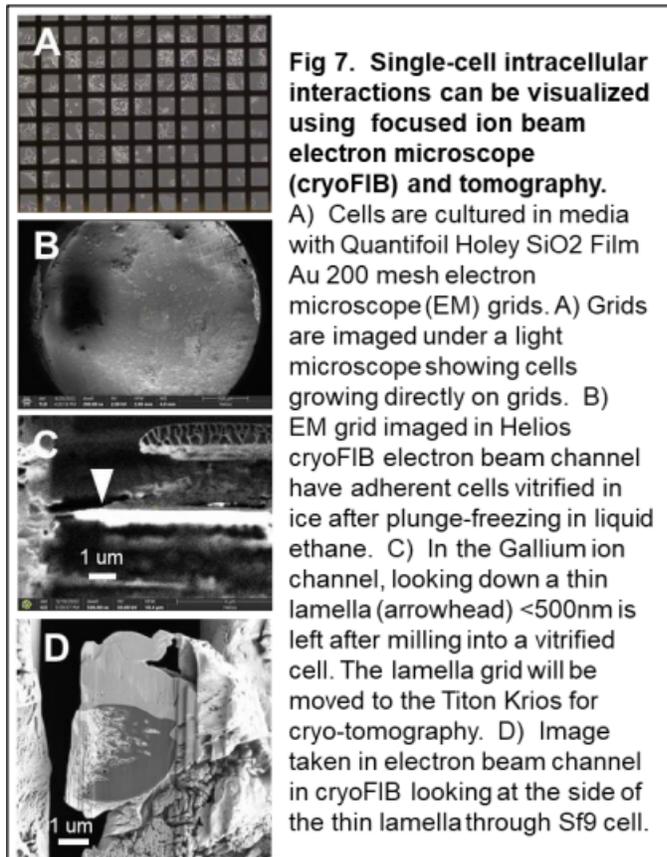


Fig 7. Single-cell intracellular interactions can be visualized using focused ion beam electron microscope (cryoFIB) and tomography. A) Cells are cultured in media with Quantifoil Holey SiO₂ Film Au 200 mesh electron microscope (EM) grids. A) Grids are imaged under a light microscope showing cells growing directly on grids. B) EM grid imaged in Helios cryoFIB electron beam channel have adherent cells vitrified in ice after plunge-freezing in liquid ethane. C) In the Gallium ion channel, looking down a thin lamella (arrowhead) <500nm is left after milling into a vitrified cell. The lamella grid will be moved to the Titan Krios for cryo-tomography. D) Image taken in electron beam channel in cryoFIB looking at the side of the thin lamella through Sf9 cell.

Specific Aim 2: Observe Tau aggregate polymorphs interactions within a cellular context. We aim to directly image Tau aggregates in cell culture models and human tissue samples derived from AD brain. We hypothesize that we will see disease specific structural changes such as Tau aggregate complex interactions, ribosomal induction and phase transitions. We can accomplish this using high pressure freezing of tissue in addition of plunge-freezing of thin tissue samples. The cryo- focused ion beam electron microscope (cryoFIB) at ASU began operation early this year and we have succeeded in development of a workflow for collecting tomography data. Cells grown on grids are plunge frozen and milled using gallium ion beam under cryo conditions to create thin lamella through individual cells. Lamellae are milled at a shallow angle through the grid after which lamellae and grid are carefully shuttled under cryo conditions to the Titan

Krios cryoEM for tomography and subsequent 3D reconstruction of the intracellular space captured in a lamella. We are currently establishing cryoFIB parameters suitable for our specific needs (Fig 7A-D) and have successfully milled lamellae through an SH SY5Y cell and an insect cell (Fig 7CD) suitable for cryo-tomography scheduled in late May 2022. We have now added to our structural methods, serial slice-and-image of larger tissue sections using the cryoFIB which can be accomplished after high-pressure freezing. A new high-pressure freezer is in the commissioning phase and scheduled to operate in July 2022.

Specific Aim 3: Study of phosphorylation forces key to tau polymorph formation. We aim to study how different phosphorylation patterns affect the folding of Tau protein in our cellular models. We have established Tau expression in our models, and by mass-spectrometry services, we will map the posttranslational modifications occurring within the cells as a baseline landscape before we begin to study intracellular microenvironment changes

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Outreach, Recruitment, and Ongoing Engagement of Latino Research Participants. David W. Coon, PhD, Jessica Langbaum, PhD, Richard Caselli, MD, Thomas Beach, MD, PhD, Alireza Atri, MD, David Weidman, MD, Anna Burke, MD, Steven Rapcsak, MD, Eric Reiman, MD. Arizona State University; Banner Alzheimer's Institute; Mayo Clinic Arizona; Banner Sun Health Research Institute; Barrow Neurological Institute, University of Arizona; Arizona Alzheimer's Consortium.

Specific Aim:

- 1) Support new outreach and community engagement strategies to increase engagement, enrollment, and retention efforts of Latino participants.

Background and Significance:

This proposal requests complementary support to enhance ongoing efforts for participant recruitment and outreach efforts as part of the Arizona Alzheimer's Consortium's ADC and ancillary programs. The Arizona ADC is part of a multi-institutional state-wide consortium that links together the major research institutions in Arizona to advance effort in the early detection, tracking of progression, and evaluation treatments and prevention therapies for Alzheimer's disease and related disorders. The ancillary programs include the Arizona BBDP and Arizona APOE4 Gene Dose Program. The Arizona Brain and Body Donation Program (BBDP) provides an invaluable scientific resource of longitudinal cognitive, motor, clinical, and genetic data from >800 living older adults who have standardized annual assessments, consent to brain (and frequently body) donation, and provide a resource of unusually high-quality brain tissue, postmortem CSF and blood samples (which differ in some respects to samples that are acquired in life) and neuropathological data after they die. The program includes but is not limited to research participants with the clinical features of Alzheimer's disease (AD) or related disorders and cognitively and neurologically unimpaired older adults with support from the National Institute on Aging (NIA)-supported Arizona ADRC Core Center (ADRCC), research participants with the clinical features of Parkinson's disease (PD) and related disorders and cognitively and neurologically unimpaired older adults with support from the National Institute of Neurological Disorders (NINDS)-supported National Brain and Tissue Resource for PD and Related Disorders (NBTR-PD). The Arizona APOE4 Gene Dose Program provides an invaluable scientific resource of longitudinal data from initially cognitively unimpaired research participants with two, one and no copies of the APOE4 allele, the major genetic risk factor for AD. The program includes nearly 200 participants who were initially late-middle-aged participants with a first-degree family history of dementia who are followed every two years with a battery of clinical ratings, cognitive tests, FDG, amyloid and now tau PET scans, and MRIs, who have provided plasma, serum and PBMC samples that are stored at Mayo Clinic, and who have begun to provide CSF samples with support from a longstanding NIA grant. It also includes more than 200 other participants, with or without a family history and through youngest to oldest adult ages, who are followed using state and organizational Arizona Alzheimer's Consortium funds, and who have not yet provided CSF, plasma and serum samples.

Latino Recruitment, Enrollment: The inclusion of Latino participants from a variety of backgrounds and different characteristics (e.g., level of educational attainment, race, country of origin, family history of AD) will assist investigators in providing answers to questions about dementia diagnosis, treatment, and management strategies that are likely to be applicable to the broad U.S. population. Additionally, a more diverse participant pool will facilitate investigations of different

risk factors, health disparities and the neuropathology and genetics of AD and related dementias as well as studies of caregiving and family burden in diverse groups.

Preliminary Data and Plan:

Outreach and Recruitment. Discussions with leadership at various Consortium sites continue to generate ways to strengthen and advance new outreach strategies through partnerships with larger online research projects with substantive Latino enrollment (e.g., MindCrowd), online and on-the-ground research projects (e.g., All of Us), and community engagement programs involving community health workers and *promotores*. However, there is a need to complement these efforts and approaches with additional professional marketing methods to extend the AAC's engagement of the Latino community and to recruit and retain a larger, more diverse pool of Latino participants.

Proposed One-Year and Long-Term Outcomes:

The proposed outcomes would be to increase Latino enrollment and retention into the ADRC Core and its ancillary programs and identify new ways to foster sustained engagement of the Latino community. Funds will be used in a way that complement but do not overlap with funding provided by the NIA and other funding sources for the ancillary programs.

Year End Progress Summary:

Outreach efforts during the past year encompassed a combination of in-person events, traditional media, and social media strategies. As a result of the COVID-19 pandemic, we have adapted our activities to include video conferencing (i.e., Zoom), Facebook and Facebook Live events, texting, and the like to reach these populations. On-the-ground efforts progressed through local community health worker/*promotores* programs such as the HOPE Network in coordination with Dr. Coon's team. The team provided outreach and educational presentations to over 1,400 Latino participants about cognitive aging, dementia, and family caregiving issues with attention paid to AAC partner offerings, resources, and research opportunities. Community education presentations have been offered at HOPE Network meetings, in partnership with a variety of community-based organizations (e.g., local area agencies on aging, the Alzheimer's Association) as well as individualized Zoom-based and in-person presentations to numerous organizations from *Salud en Balance*, El Rio Health, Muhammad Ali Parkinson's Center, the Parkinson's Foundation, and *Consulado Mexicano* to Tempe Action Alliance, American Heart Association, *Si Se Puede*, United Health Care, MAG Transportation Ambassadors, Equality Health and local church and senior centers). Social media outreach efforts included Facebook Live Events on multiple bilingual health/culture pages, bilingual newspapers/magazines, radio shows for the Latino community (e.g., *Entre Mujeres*, AARP Latino station, *La Reyna*). Outreach on social media also heavily relies on cross-promotion from our community partners; and there have been ongoing discussions with MindCrowd and All of Us about ways to target Latino/Hispanic and Native American participants to encourage enrollment in Arizona Alzheimer's Consortium activities. While it took some time, we were able to identify and secure a local professional marketing firm with established experience in the Latino community. The firm worked with us to develop a campaign and related assets that leverage both traditional media and social media venues to engage, recruit, and retain Latino participants in ADRC research. Products included commercials, social media posts (static ads, stories, and look live videos"), and the initial distribution plan of assets for a campaign in English. These assets and plan can be effectively coordinated with a future companion campaign in Spanish. Some materials are still being reviewed by AAC leaders for final distribution.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Arizona Alzheimer's Consortium (AAC) Website Updates. David W. Coon, PhD (PI), Jessica Langbaum, PhD. Arizona State University; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Project Description:

The Arizona Alzheimer's Consortium (AAC), including through website operations, is home to the nation's leading model of a statewide collaboration in AD research. As an umbrella organization, the AAC consists of many stakeholders and includes the Arizona Alzheimer's Disease Research Center (ADRC), which involves AAC member institutions and their researchers and is sponsored by the National Institute on Aging. The collaborative work of the Arizona ADRC plays a pivotal role in the success of the AAC. The enhancement of website operations benefits AAC, consortium member institutions, and other AAC stakeholders through increased interoperability, accessibility, and web-based information sharing activities among consortium members and other AAC stakeholders involved in new and existing Alzheimer's disease (AD) research opportunities and findings advanced by the AAC. Non-match funds will facilitate these enhancements, to include user-friendly web-based portals that provide functionality to help (a) manage secure requests for data and sample sharing, (b) ease participant recruitment and enrollment into AAC research studies, (c) highlight AAC partner education activities and products for Arizona families and other stakeholders across our communities, (d) foster communication among our interdisciplinary groups of researchers, and (e) advertise opportunities for new investigators and interested students to engage with the AAC and its member institutions. The website enhancements and updates will be interconnected and will help highlight the AAC "Cores" as outlined by the ADRC (i.e., Administrative, Clinical, Data Management and Statistics, Neuropathology, Outreach, Recruitment & Engagement) and our Research Education Component that is dedicated to building the pipeline of future investigators. The website will allow researchers inside and outside of the consortium (including those with state-supported research projects), to learn about other researcher's expertise, ways to access shared resources of data and biological samples, and our research, outreach, education and training programs available to researchers, trainees, and students. Access to this information will increase productivity and impact in our fight against AD and related dementias and help to fulfill our Consortium's goals. Finally, these funds will support ongoing website updates to maintain latest website standards (including security standards) for AAC and its consortium members.

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: continuing web development work, such as usability and platform testing to ensure the sites work on common browsers and devices (desktop, laptop, and mobile), and 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; establishing a Vimeo social media channel with more than 630 minutes (10.5 hours) of presentation content to date 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 already shared with the AAC website has achieved 6,286 impressions (meaning at least partial views) from Sept 30, 2021 – August 8, 2022. Additional content that is currently under review and being published to the websites includes more than 270 minutes (4.5 hours) of presentations from the 2021 AAC Scientific Conference) and other recent presentations from our scientists; more than 200 new graphics and images sourced for use; and drone footage of our communities to emphasize the far-reaching effect of our multi-site statewide presence. Video footage and interviews from 2022 AAC Scientific Conference will be published as well.

Key content is being targeted for translation 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 available for repurpose into additional social media campaigns.

Longer term 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; and ongoing art direction and graphic design that strengthens branding between the AAC and the ADRC sites and our member institutions, and enhances community engagement. Therefore, 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.

**BANNER ALZHEIMER'S INSTITUTE
PROJECT PROGRESS REPORTS**

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Advanced Imaging and Machine Learning in Alzheimer's Research. Yi Su, PhD, Hillary Protas, PhD, Michael Malek-Ahmadi, PhD, Valentina Ghisays, PhD, Yinghua Chen, MS, Ji Luo, MS, Wendy Lee, MS, Alireza Atri, MD, PhD, Thomas G. Beach, MD, PhD, Teresa Wu, PhD, Kewei Chen, PhD, Eric M. Reiman, MD. Banner Alzheimer's Institute; Arizona State University; University of Arizona; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Specific Aim(s):

- 1) Specific Aim 1: To further develop and validate machine learning (ML) and deep learning (DL) techniques for data harmonization, missing data imputation, and prediction of disease progression.
- 2) Specific Aim 2: Continued development of robust and high throughput image analysis pipelines that allow large scale data analysis.
- 3) Specific Aim 3: To further investigate white matter (WM) and metabolic changes of the brain in AD and aging.
- 4) Specific Aim 4: To introduce and implement advanced statistical methodologies such as SEM (structural equation modeling), especially the latent growth curve analysis, and GEE (generalized estimating equation for inference especially at the population level) for their use in AD neuropathological, behavior and biomarker investigation.

Background and Significance:

AD is characterized neuropathologically by extracellular amyloid accumulations and intracellular tangles of hyperphosphorylated tau protein (1), both of which can now be measured in vivo using positron emission tomography (PET) imaging (2, 3). In addition, 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 can be measured and monitored in vivo using either PET (4-6) or magnetic resonance imaging (MRI)(7-11). Reliable quantifications of these pathological events using imaging techniques are critical to the better understanding of AD and the development of successful management strategies. However, several technical hurdles are hampering the optimized utilization of imaging and biomarker data to investigate AD and developing treatment strategies. a) Heterogeneity in imaging protocols, radioligands, and quantification methodology for PET and MRI lead to inconsistent quantitative measurements; b) The ever-expanding imaging datasets requires robust streamlined processing and analysis pipelines; c) Advanced imaging techniques to track white matter and metabolic changes of the brain are underutilized while they may provide important information about disease state; and d) To better characterize complicated relationship among numerous factors for the longitudinal change till death (with neuropathological data), more advanced statistical tools are needed. We aim to address these challenges in this year's methodological development efforts and making tools available to the local and external research.

Experimental Designs and Methods:

Aim 1: a) We will further investigate the use of ML and DL techniques to harmonize PET imaging data from different tracers; b) We will also investigate the application of DL based technique in synthetic imaging applications such as missing imaging modality imputation; c) We will continue to investigate ML and DL techniques in applications such as predicting amyloid positivity from MR, estimating biological age from imaging data, and prediction of disease progression based on imaging data.

Aim 2: We will further integrate FreeSurfer-based individual space processing/analysis pipelines with SPM-based template space pipelines and address problems such as a) MR free analysis of PET data in both individual and template space and obtain harmonized results vs. MR dependent pipelines; and b) automated imaging and analysis result QC to reduce the need of human intervention and increase throughput.

Aim 3: a) We will further characterize WM signal in amyloid PET imaging and its relationship to white matter integrity, aging, and cognitive performance; b) We will leverage ML/DL techniques to derive or impute perfusion, metabolism, and blood-brain barrier related measurements and investigate their relationship with aging, cognitive performance, and AD specific pathologies.

Aim 4: We will adopt the SEM, latent growth curve analysis, and GEE procedure in matlab and R, test and validate their use, and apply them to our ongoing research especially for data from our colleagues at Banner Sun Health Research Institute.

Proposed One-Year and Long-Term Outcomes:

In the upcoming year, for Aim 1, we anticipate completing our preliminary investigation of ML and DL techniques to harmonize FBP and PiB imaging data and publish the results in peer reviewed articles. These results will help with our effort to resubmit our R01 application on the development of multi-tracer PET harmonization techniques. We also anticipate generating preliminary results demonstrating the feasibility and utility of DL techniques in missing data imputation applications. For Aim 2, the streamlined processing pipeline will be implemented which will facilitate our STTR collaboration and the API-ADAD trial data analysis. For Aim 3, we expect to have at least one manuscript submitted for publication and generate additional preliminary data that may allow us to seek extramural funding to expand our research. For Aim 4, we plan to implement, test and validate the advanced multivariate statistical pipelines in R, MATLAB or both. In long term, we aim to further strengthen our imaging, statistical and AI expertise and build a cluster of advanced tools that facilitate the investigation of AD and related disease and the successful development of disease modifying treatments and continue to pursue extramural fundings to allow expansion of our methodology development efforts.

Year End Progress Summary:

In this funding period, the CIAL team continue to develop advanced data analysis methodologies and machine learning techniques to facilitate AD research.

For Aim 1, continuing our previous efforts in the development of PET harmonization techniques, we completed our first manuscript summarizing a Residual Inception Encoder Decoder network (RIED-Net) model that takes a florbetapir (FBP) scan and generates synthetic Pittsburgh Compound B (PiB) images for improved cross-tracer harmonization. The deep learning model was trained on a cohort of 92 participants from the Open Access Series of Imaging Studies (OASIS) and tested on an independent cohort of 46 participants from the Centiloid Project website. The model achieved significantly stronger between-tracer agreement ($p < 0.001$) for both global amyloid burden and voxel-wise measurements. This manuscript was recently published (Shah et al., Alzheimer's & Dementia 2022). One issue related to this PET harmonization effort is the limited head-to-head tracer comparison data currently available. To address this issue, we are currently exploring transfer learning (TL) as an approach to leverage existing data from different sources and unpaired amyloid PET data. In a preliminary investigation of the TL approach, we compared the model trained directly on a small dataset of PiB-florbetaben (FBB) pairs (N=35) to the model initially trained on the above mentioned the larger OASIS PiB-FBP dataset (N=92) and subsequently fine-tuned on the PiB-FBB dataset (the TL approach). We found the model obtained from the TL approach achieved numerically better agreement (although not statistically significant). This demonstrates the potential of the TL approach in addressing the data

shortage issue. This work will be presented in the upcoming AAIC 2022 conference. Our team is also examining an alternative strategy that focus on regional analysis using conventional machine learning techniques. This approach also demonstrated promising results in improving the agreement between global amyloid measures. A manuscript is currently under preparation. This research contributed to our recent R01 application (1R01AG032424-01A1) which received a fundable score (18%), and we anticipate receiving the award notice this summer.

Another related line of research we have been following is the use of machine learning/deep learning techniques to identify structural MR signatures of brain aging. We previously demonstrated a model incorporating these signatures and the subsequently estimated brain age can be leveraged to differentiate AD diagnostic groups (Gao et al. *NeuroImage: Clinical* 2020). Recently, we implemented a 3D deep ResNet model which achieved improved performance in age prediction with a mean absolute error of 3.76 years. We also demonstrated that the difference between MR estimated age and chronological age increase in the order of normal control < normal-to-MCI converter < MCI < MCI-to-AD converter < AD patients, as expected. This finding provides evidence supporting the hypothesis that the impact of AD pathophysiology and disease progression can be interpreted as accelerated aging. This work will also be presented at the upcoming AAIC 2022 conference, and we will continue to expand research in this direction.

For Aim 2, we continue to streamline our image preprocessing/analysis pipelines. With support from this award and two NIH sponsored projects (R01AG058468 and R42AG053149), an integrated pipeline for T1 MRI and PET analysis was implemented and applied to the ADNI cohort and the API-ADAD trial imaging data. The pipeline included rigid alignment of individual T1 MRI to the template space followed by FreeSurfer (v7.1) and CAT12 analysis, PET images were then processed with reference to FreeSurfer defined regions followed by spatial normalization using CAT12 defined deformation field. This pipeline defines brain regions in individual and atlas space, transforms imaging data into MNI152 template space using DARTEL based spatial normalization field, generates gray matter, white matter density maps in both individual and template space, generates regional PET measures with and without a regional-spread-function (RSF) based partial volume correction, and generates PET SUVR images with default cerebellum reference region in both individual (MR) and template space. An extension to this pipeline also allows the inferior cerebellum regions for improved tau PET quantification. Using this integrated pipeline, a total of 4775 T1 scans, 2521 FBP scans, 2051 FDG scans, and 1157 FTP scans have been processed from ADNI under this project together with R42AG053149 in the past year. The same pipeline is also currently applied to process data from other projects including R01AG058468 (API-ADAD), R01AG069453 (APOE), P30AG072980 (Arizona ADRC), and legacy data from previous projects.

For Aim 3, one manuscript currently under revision summarizing the findings based on Knight ADRC imaging data demonstrating white matter amyloid PET tracer (PiB) uptake decreases with age cross-sectionally, and longitudinally. We are expanding the analysis of amyloid PET white matter signal to ADNI cohort. We also have Ms. Vedanshi Bhargava, an MD/PhD student from UA-SOM-P, joining our team and will carry out further research under this theme using independent funds.

For Aim 4, SEM models were implemented and applied to ongoing research in collaboration with BSHRI investigators. The prespecified analysis did not generate positive findings. However, the model implementation in R/MATLAB and JASP will be available for future research projects.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Native American Outreach, Recruitment, and Retention Program. David Weidman, MD, Lori Nisson, LCSW, Richard Caselli, MD, Alireza Atri, MD, PhD, Eric M. Reiman, MD, Pierre N. Tariot, MD, Jennifer Craig-Muller, and David Coon, PhD. Banner Alzheimer's Institute; Mayo Clinic; Banner Sun Health Research Institute; Arizona State University; University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

1. To forge a close working relationship with members of our Native American Community in the awareness, care, and scientific understanding of Alzheimer's disease (AD) through educational and service-related outreach activities.
2. To support the participation of interested Native Americans in the ADRC clinical core and research studies of interest to them without detracting from our other outreach and partnership-development goals.
3. To work with partners that specialize in Native American recruitment to increase Native American enrollment to advance AD research from this understudied, underserved population.
4. To create novel opportunities to reach tribal community members through education, support and sharing current information about advancing research.

Background and Significance:

Native Americans facing the problem of Alzheimer's disease (AD) constitute the most underserved 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 they participate in research studies. We have continued to attract a number of interested participants from the Urban Native American community to participate in the Arizona Alzheimer's Disease Research Center (ADRC) Clinical Core. In addition, we recently partnered with Medstar who operate the Strong Heart Study in Phoenix and have strong relationships with the urban Native American Population. Through the partnership, Medstar educates their community about research and facilitates enrollment (scheduling and transportation) for those who are interested.

Preliminary Data:

A cumulative 101 Native Americans have been enrolled across the consortium as of April 2022 of those 101, 64 are currently included in the NACC database. Overall, there are 45 active NA ADRC participants, and 56 are inactive. There are 37 actively enrolled at Banner Alzheimer's Institute (BAI).

As a result of the COVID 19 pandemic, presentations and outreach activities have been limited in tribal communities. There have been many changes within these programs that provide education and support services to elders and family caregivers. Many tribes have been working to sustain their communities with basic needs, manage complex and challenging circumstances and remain connected with limited internet access. Given these circumstances, the outreach team has pivoted and restructured efforts in collaboration with departments that serve aging populations to balance tribal community priorities.

Due to safety concerns, the 16th Annual Conference on Native Americans and Alzheimer's disease was postponed and is planned for October 2022 at the Ak-Chin Community in Maricopa,

AZ. The Native American outreach team will provide training to more than 100 professional care providers during this time through virtual programs including a Native American and Alzheimer's disease toolkit training. As conditions improve, the outreach team plans to resume in person on tribal lands.

Despite pandemic conditions, the Native American outreach team continues to find innovative ways to reach tribal community members, providing: 1) a BAI Native American Beacon e-newsletter distributed to more than 700 professionals, family caregivers, and community members; 2) printed quarterly Native American Beacon newsletters distributed to human services, senior centers and health care centers to augment accessibility; 3) a monthly Native American Circle discussion group, providing information and support for caregivers and community members from Arizona tribal communities; 4) a dozen community homes delivered meals and meal pick up programs throughout Arizona's tribal nations; 5) connection with tribal families living with dementia to provide our Native American Navigating Memory Loss guides. The team has been collaborating with tribal partners and Canyon Records tribal music production company to create a CD of classic American Southwest tribal music to provide life enrichment for persons with dementia and family caregivers with an informational insert to offer techniques to minimize behavioral challenges and improve quality of life at home.

The partnership with Medstar, the local partner for the Strong Heart Stroke Study, has been invaluable to meet enrollment goals; almost all the new Native American enrollments that occurred in 2020-2022 were a result of a Medstar referral. Medstar maintains an active database of Native Americans that are interested in participating in research and provides regular communication to those in the database. Pairing each referral with an outreach coordinator who supports the participant throughout the enrollment process provides the participant with a trusted resource, which contributes to the higher conversion rate compared to general outreach. The overall willingness to participate in research has increased in the Native American community during the COVID-19 pandemic and Medstar has seen an increase of people joining their referral database. We have extended our partnership with Medstar and will continue to utilize their expertise to increase enrollment into the ADRC. The retention rate of Native American participants who enrolled in 2019-2020 is over 90%. We attribute this to the support and ongoing education that Medstar provides to participants after they enroll.

To help facilitate remote visits for participants that are hesitant or cannot travel to BAI to complete their research visit, we updated our protocol to allow for phone consenting and completion of study procedures. The phone study visit is shorter, which decreases the overall participant burden. We will continue offering the remote option to Native American participants. Using complimentary funds, we also provide financial support for costs associated with participating in the ADRC including overnight hotel stays, mileage reimbursement, and meal per diems.

Proposed One-Year and Long-Term Outcomes:

1. Continue outreach efforts to general Native American communities and education of health care providers for American Indians that will decrease the disparity related to diagnosis and treatment of AD and related disorders in both reservation and urban dwelling Natives.
2. Help to recruit and retain Native Americans into the ADRC Core, such that we are following >50 actively enrolled NAs at BAI, and >75 NAs at all our clinical core sites by July 2023, capitalizing in part on emerging relationship with our colleagues from Medstar
3. Refine methods to reach more Native Americans from youth to elders to raise community awareness by offering quarterly virtual education programs.

4. 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 an annual BAI Native Americans and Alzheimer's disease: Tools for the Care Provider toolkit training.

Funds will be used in a way that complement but do 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)

Year End Progress Summary:

Aim 1: During the past year, education and outreach activities have reached more than 700 professionals, family caregivers, and community members from Native American tribal communities across Arizona. Despite pandemic conditions, the Native American outreach team continued to find innovative ways to reach tribal community members, to provide informative and culturally sensitive newsletters and memory loss educational guides, and to hold discussion groups. We have collaborated on a musical project with tribal partners and Canyon Records tribal music production company to create a CD of classic American Southwest tribal music to provide life enrichment for persons with dementia and family caregivers.

Aim 2: During the 2021 calendar year and the first half of 2022, for the Native American cohort, across the consortium, we enrolled 9 new participants, 45 initial and follow-up assessments were conducted, 6 participants were withdrawn, and 2 participants died. We will continue to work with the ADRC Education Core to find ways to optimize retention in our longitudinal research program. With our SHSS partnership, and resumption of in-office participant visits, we anticipate recruiting and retaining interested Native American participants at a greater frequency the remainder of 2022. We have continued to reach participants through community outreach, anticipate community events to resume should pandemic restrictions lift, and we have begun to explore new relationships with partnering organizations to help in the recruitment, retention, and productive study of Native American research participants.

Aim 3: BAI Native American Program has received funding from the May and Stanley Smith Charitable Trust for NA Outreach, and the John and Sophie Ottens Foundation, to support development and advancement of culturally sensitive Native American outreach, education, and support programs.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Alzheimer's Prevention Registry. Jessica B. Langbaum, PhD, Eric M. Reiman, MD, Pierre N. Tariot, MD. Banner Alzheimer's Institute; Arizona Alzheimer's Consortium; University of Arizona; Arizona State University.

Specific Aims:

Aim 1: To increase enrollment into the Alzheimer's Prevention Registry, particularly within Arizona.

Aim 2: To increase the number of study opportunities available to Alzheimer's Prevention Registry members, particularly within Arizona, by pilot testing 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 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 impact¹. 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 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 enrollment², with 30% under-enrolling and only 7% of sites enrolling the projected number of participants in their originally stated timelines³. Delayed or inefficient recruitment has scientific, financial, and ethical consequences⁴. 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 recruit, engage, and retain participants, with particular attention to recognizing the needs of underrepresented diverse populations effectively and efficiently. 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 studies⁵. 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. As enrollment in the Registry and its GeneMatch program continues to increase, it is imperative that we expand the number of and types of study opportunities available to participants, particularly within Arizona, and provide initial metrics of success at connecting Registry/GeneMatch participants with study opportunities, particularly within Arizona. The results from this effort will help accelerate enrollment into critically important AD-focused studies, particularly within Arizona.

Preliminary Data:

As of April 2021, more than 350,000 individuals have joined the Registry. 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 (50%) (12% are unsure and 18% prefer not to answer) and self-report not having a diagnosis of cognitive impairment (94%). As of April 2021, the Registry has helped recruit for 131 studies and is currently assisting with recruitment for 46, including 19 Arizona-based studies. We are in the process of onboarding several new studies, including studies taking place in Arizona. The Registry email newsletters are well-received, with an average open rate of 38.7%, and unique click rate of 12.2% 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 38.1% and unique click rate of 12.6%. In 2019 we received an R01 grant from the NIA (R01AG063954; “Establishing the science behind Alzheimer's recruitment registries: opportunities for increasing diversity and accelerating enrollment into trials”), and in 2020 we received a two-year supplement to the R01 to examine the intersection of two critical sources of messaging that may influence perceptions of scientific research and AD and well as adherence to recommended behaviors for preventing COVID-19: family members/adult children of older adults and mass media. Also, in 2019 we received a SBIR grant from the NIA (1R43AG055218; “Improving Mobile Access for Recruiting Study Volunteers from Underrepresented Populations for Alzheimer's Disease Research and Other Studies”), each of which will provide necessary data to inform strategies to increase participation of men and individuals from underrepresented racial and ethnic groups in AD-focused registries and studies. We recently submitted a revision to our R33 application to the NIA, entitled “Optimizing research infrastructure of registries to accelerate participant recruitment into Alzheimer's-focused studies” which received a favorable score and will be reviewed by Council in May 2021.

Experimental Designs and Methods:

To achieve Aim 1, we will work to expand Registry enrollment in Arizona through community outreach efforts and promotion on social media, tracking the success of each strategy and tactic. Concerted efforts will be made to increase the enrollment of individuals from underrepresented populations, particularly of individuals who identify as Hispanic/Latino and African American.

To achieve Aim 2, we will work with Arizona ADRC and AAC researchers to promote their studies to APR 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.

To achieve Aim 3, we will provide initial metrics of success at connecting Registry 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 Registry to accelerate enrollment.

Proposed One-Year and Long-Term Outcomes:

Results from this effort will help demonstrate the effectiveness of the Registry 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:

The Alzheimer's Prevention Registry is an online community of individuals age 18 and older who agree to receive emails with information about Alzheimer's prevention related research updates as well as notifications about study opportunities within their communities⁵. GeneMatch is open to adults ages 50-90 who live in the United States and report not having a diagnosis of cognitive

impairment⁶. As of June 2022, the Registry had over 380,000 members and GeneMatch enrolled over 100,000. In August 2021 we were awarded a R33 grant from the NIA, entitled “Optimizing research infrastructure of registries to accelerate participant recruitment into Alzheimer’s-focused studies” (R33AG070604-01A1). The R33 will incorporate findings from our R01 (R01AG063954), which is focused on understanding the facilitators and barriers for men, Hispanic/Latino, and Black/African Americans to joining a participant recruitment registry, as well as data from our recently completed Phase 1 of our 1R43AG055218; “Improving Mobile Access for Recruiting Study Volunteers from Underrepresented Populations for Alzheimer’s Disease Research and Other Studies. Manuscripts describing data from the R01 and R43 are currently under review for publication in peer-reviewed journals.

Aim 1). During the funding period, considerable effort was undertaken to increase enrollment into the Alzheimer’s Prevention Registry (APR) and its GeneMatch program as well as to maintain engagement of existing members. During the funding period, nearly 30,000 new people joined APR and 10,000 people joined GeneMatch. As of June 2022, a total of 19,496 APR members and 9,706 GeneMatch members indicate they live in Arizona. Successful enrollment strategies include advertising on social media channels (e.g., Facebook) and direct referral/word of mouth from existing members. Engagement with members remains. Members are opening and reading their emails from our program. For example, our monthly newsletter had an average open rate of 36.3%, and unique click rate of 5.7% in the past 12 months, compared to the industry standard of 16% and 1.6%, respectively.

Aim 2). The APR has helped recruit for more than 152 AD-focused studies since its inception. Currently, we are assisting with 35 studies, including 8 Arizona-based studies and 15 studies taking place online and open to Arizona residents. Since its launch, GeneMatch has helped recruit for 18 studies, including 4 studies led by Arizona investigators with several other being multisite studies with AAC partner institutions serving as performance sites. During the funding period we developed and began initial pilot testing of an AAC/ADRC scholarship application to provide recruitment support for new / junior AAC/ADRC investigators or for pilot studies being conducted by AAC/ADRC investigators in preparation for an NIH grant submission. Five AAC/ADRC investigators reached out to the APR and/or GeneMatch about our recruitment resources during the funding year.

Aim 3). The APR and GeneMatch help with recruitment in a variety of ways. One path is sending emails to members about a particular study opportunity and asking the member to “accept” the invitation and share their contact information with the enrolling study for further screening (using the contact form described below). For the APR, study opportunity emails had an average open rate of 32.0% and unique click rate of 3.0% during the funding period. A second path (which is only available for the APR as GeneMatch requires direct matching / invitations) is listing the study opportunity on the APR website’s “Find a Study” section. The listing includes a form that can be filled out by the interested website visitor with their name, email address and phone number, review and acknowledge the study’s eligibility criteria and authorization for APR to share their contact information with the enrolling study team. Not all studies have rolled over to this “contact form” model (e.g., some are still grandfathered to our prior model which asked participants to call/email the enrolling study site directly). During the funding period, 26 studies were using the contact form model, including 11 Arizona-based studies (not including multi-site studies with an Arizona location). During the funding period we sent 2259 referrals (978 to Arizona sites) to these studies that are using the contact form. As a reminder GeneMatch invites selected members to studies based on a study-specific algorithm which may include variables such as age, APOE genotype, sex, family history of dementia, etc. GeneMatch has helped 3 Arizona-based studies with recruitment (not including multi-site studies with an Arizona location), inviting 5,485 individuals to those studies.

References:

- 1 Brookmeyer, R., Gray, S. & Kawas, C. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. *Am. J. Public Health* **88**, 1337-1342 (1998).
- 2 Dowling, N. M., Olson, N., Mish, T., Kaprakattu, P. & Gleason, C. A model for the design and implementation of a participant recruitment registry for clinical studies of older adults. *Clin. Trials* **9**, 204-214, doi:1740774511432555 [pii];10.1177/1740774511432555 [doi] (2012).
- 3 Strasser, J. E., Cola, P. A. & Rosenblum, D. Evaluating various areas of process improvement in an effort to improve clinical research: discussions from the 2012 Clinical Translational Science Award (CTSA) Clinical Research Management workshop. *Clin. Transl. Sci* **6**, 317-320, doi:10.1111/cts.12051 [doi] (2013).
- 4 Gul, R. B. & Ali, P. A. Clinical trials: the challenge of recruitment and retention of participants. *J Clin. Nurs* **19**, 227-233, doi:JCN3041 [pii];10.1111/j.1365-2702.2009.03041.x [doi] (2010).
- 5 Langbaum, J. B. *et al.* The Alzheimer's Prevention Registry: a large internet-based participant recruitment registry to accelerate referrals to Alzheimer's-focused studies. *J Prev Alz Dis* **7**, 242-250, doi:10.14283/jpad.2020.31 (2020).
- 6 Langbaum, J. B. *et al.* GeneMatch: a novel recruitment registry using at-home APOE genotyping to enhance referrals to Alzheimer's prevention studies. *Alzheimer's and Dementia* **15**, 515-524, doi:<https://doi.org/10.1016/j.jalz.2018.12.007> (2019).

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

APOE4, Vascular Risk, and AD Biomarkers in PSEN1 E280A Carriers and Controls. Jeremy Pruzin, MD, Kewei Chen, PhD, Eric Reiman, MD, Yi Su, PhD, Yakeel Quiroz, PhD, Kaj Blennow, MD, PhD, Oskar Hansson, MD, PhD, Kenneth Kosik, MD. Banner Alzheimer's Institute; Arizona Alzheimer's Consortium; Arizona State University; University of Arizona; Massachusetts General Hospital, Harvard Medical School; University of Gothenburg; Lund University; University of California.

Specific Aim(s):

The goal of this proposal is to examine how two common risk factors for Alzheimer's disease (AD), APOE4 and systemic vascular risk, affect plasma concentrations of three promising plasma AD biomarker candidates: neurofilament light (NfL), phospho-tau 217 (p-tau 217), and beta-amyloid 42/40 (A β 42/40) in middle-aged cognitively unimpaired PSEN1 E280A mutation carriers (mean age 37) and age-matched non-carrier controls (mean age 34).

Aim 1. Determine whether the presence of at least one copy (homozygotes and heterozygotes) of APOE4 is associated with abnormal levels of plasma concentrations of NfL, p-tau 217, and A β 42/40 in both cognitively unimpaired PSEN1 E280A adult mutation carriers and age-matched non-carrier controls.

Aim 2. Determine whether degree of systemic vascular risk, quantified with the Framingham Heart Study cardiovascular disease risk score (FHS-CVD),¹ is associated with abnormal levels of plasma NfL, p-tau 217, and A β 42/40 in both cognitively unimpaired PSEN1 E280A adult mutation carriers and non-carrier controls.

Aim 3. Examine the interactive effects of the presence of the APOE4 allele with degree of systemic cardiovascular risk on plasma concentrations of NfL, p-tau 217, and A β 42/40 in both cognitively unimpaired PSEN1 E280A adult mutation carriers and non-carrier controls.

Background and Significance:

The pathophysiological process that results in an eventual diagnosis of symptomatic AD is increasingly thought to transpire over the course of decades, not years. This has led to speculation that interventions during the long preclinical period may be more effective in addressing the disease. Additionally, many factors influence an eventual diagnosis of AD dementia other than the aggregated proteins A β and tau, with degree of vascular risk emerging as one of the more important additional factors. Evidence is abundant that both the AD pathophysiological process is ongoing in middle age and that degree of vascular risk is a significant contributor to the process. Healthy APOE4 carriers aged 20-39 have a similar pattern of hypometabolism on FDG-PET as patients with AD dementia.² The presence of two or more vascular risk factors in midlife is associated with about a 3-fold increased odds of brain A β deposition later in life (median follow up 23.5 years) in APOE4 non-carriers and over a 9-fold increase in APOE4 carriers.³ Mild elevations in blood pressure are associated with smaller gray matter volumes in AD-relevant brain regions in 19-40 year-olds⁴ and the presence of stage one or stage two hypertension in midlife are associated with an 18% and 25% increased risk of AD dementia later in life respectively.⁵ While there is good evidence that the AD pathophysiological process is ongoing during midlife, there is at present no practical method to detect or track early changes that indicate increased risk of future decline. The ideal candidate for such a method would involve one or a combination of blood-based biomarkers that are relatively non-invasive, easy, inexpensive to obtain, and can be followed longitudinally. Several promising candidates for blood-based AD biomarkers have emerged recently including NfL⁶, p-tau 217⁷, and A β 42/40⁸, although study of these biomarkers

has thus far focused on making accurate diagnoses in older persons. It remains unknown whether these biomarkers are indicative of future risk and/or will have utility in detecting and tracking risk of future cognitive decline alone or in the context of other known risk factors like presence of APOE4 in cognitively unimpaired persons. However, study of the Colombian kindred with the PSEN1 E280A mutation responsible for early onset autosomal dominant AD (ADAD) suggests that NfL and p-tau 217 may show utility in these regards since both start to diverge from age-matched controls about 20 years before the median age of onset of mild cognitive impairment.^{6,9} It is yet to be determined whether degree of vascular risk or presence of APOE4 affect these biomarkers in this population. Finally, plasma A β 42/40 is among the earliest signals of abnormal A β biology in non-mutation carriers, measurably changing years before A β is detected on amyloid PET.^{8,10} A β 42/40 is essential to take into account and may also contribute to a biomarker endophenotype predictive of future AD dementia risk in middle-aged and older cognitively unimpaired individuals.

Experimental Designs and Methods:

Population: All participants would be members of the PSEN1 E280A Colombian kindred enrolled in the Colombia Alzheimer’s Prevention Initiative Registry from August 1995 to December 2018.¹¹ Participants would be 18 or older, cognitively unimpaired (defined by a MMSE¹²>26, Functional Assessment Staging Test¹³ <2, and normal performance on a modified Spanish version CERAD¹⁴ battery) mutation carriers or age and sex-matched non-carriers from the same kindred. Baseline

Table 1	Carriers	Non-carriers
	(n=365)	(n=257)
Age, median (IQR), y	37.0 (27.0-46.5)	34.0 (25.5-42.0)
Male, %	45.5	39.3
Duration of education, median (IQR), years	7.0 (4.0-11.0)	9.0 (5.0-11.0)
MMSE score, median (IQR) a	29.0 (25.0-30.0)	30.0 (28.0-30.0)
Baseline Demographics for For Existing p-tau 217 Data		

demographics for existing p-tau 217 data is provided in Table 1⁷, demographics for the remainder of the kindred would follow a similar distribution. Exclusion criteria include a history of stroke, seizures, substance misuse, or clinical diagnosis of a psychiatric or neurologic disorder that may affect cognitive, motor, or visuospatial ability.

Samples: NfL and p-tau 217 measurements would come from existing data from previously collected samples. Measurements for A β 42/40 would come from available data as well as new assays run from existing samples from frozen plasma collected in the ongoing Alzheimer’s Prevention Initiative Autosomal-Dominant Alzheimer’s Disease Trial (API-ADAD).¹⁵ Newly collected plasma may also be available from a current philanthropic effort to collect new samples from the kindred though enough data for assay goals could be produced from existing data and frozen plasma already collected through the API-ADAD clinical trial. All blood was or would be collected in the morning with participants under optional fasting in EDTA-plasma tubes, centrifuged, and frozen within 30-60 minutes of collection at -80°C. All samples undergo one freeze-thaw cycle for aliquoting purposes before the assay of interest is run. Currently available data and goals for total sample attainment are listed in Table 2. Analysis of plasma A β 40, A β 42, and NfL are performed using the Quanterix Simoa technology on a new HD-X instrument, by

Group	Data Available			Goal n			Assays Needed		
	NfL	p-tau 217	A β 42/40	NfL	p-tau 217	A β 42/40	NfL	p-tau 217	A β 42/40
Carrier	242	365	54	242	365	150	0	0	96
Non-Carrier	262	257	54	262	257	150	0	0	96

commercial kits. The method for analysis of p-tau217 is in late-stage development using a new in-house Simoa method. The assays are performed in the labs of Dr. Oskar Hansson in the Clinical Memory Research group at Lund University, Sweden (p-tau 217) and Dr. Kaj Blennow, Department of Psychiatry and Neurochemistry, University of Gothenburg, Sweden (NfL, A β 42,

A β 40). Both are ongoing collaborators, having published on the biomarkers previously with members of our study team.^{6,7,9,16}

APOE: APOE genotyping would be performed through the neurobiology lab of Dr. Kenneth Kosik at UC Santa Barbara where samples are prepared and then sent to LGC Biosearch Technologies who use a proprietary qPCR fluorescent probe-based assay for two single nucleotide polymorphisms, rs429358 and rs7412, determinative of which alleles a participant carries. Currently about 1200 APOE genotypes from the kindred are known with 264 participants having at least one copy of APOE4 in a nearly even division of mutation carriers and non-carriers. An additional 900 samples are in the process of being genotyped and should be completed by summer of this year.

Vascular risk: Vascular risk would be quantified at baseline using the well-validated BMI-based Framingham Heart Study cardiovascular disease risk score (FHS-CVD)¹ accounting for presence of hypertension, diabetes, smoking history, BMI, and age.

Data Analysis: Statistical analysis will be performed under the guidance of the Data Management & Statistics Core of the Arizona Alzheimer's Disease Research Center. Close consultation for all statistical methods and modeling will be provided by Drs. Kewei Chen and Yi Su who have previous experience in analysis of blood-based biomarkers in AD. Using the framework of a three-way (APOE4 status, vascular risk, and PSEN E280A mutation status) analysis of covariance (ANCOVA) model, we will examine the two-factorial interaction of presence of APOE4 (Aim 1) or degree of vascular risk using the FHS-CVD score (Aim 2) with PSEN E280A mutation carrier status. We note that, given our aims and hypotheses, there is no need for testing the main linear effect in the ANCOVA model. Models will be adjusted for age, education, and sex. Note that our model is flexible so that the FHS-CVD in the above interaction effect test with PSEN E280A mutation status can be continuous or categorical. Next, we will look for three factorial interaction of presence of APOE4, FHS-CVD, and PSEN1 E280A on the same biomarker outcomes (Aim 3). Thus, this three-way ANCOVA will allow for determination of between-group differences in the interactive effects of APOE4 and FHS-CVD in mutation carriers versus non-carriers. We note that the three tests above (one for each aim) are planned and traditionally statisticians do not correct for multiple comparisons for the main effects and the interactions; we will use false discovery rate to correct for multiple comparisons. For subsequent relevant contrasting testing (e.g., the directional increases of plasma NfL or p-tau 217 in unimpaired PSEN E280A adult mutation carriers who are also APOE4 carriers and with higher FHS-CVD scores as in contrast with other groups), we will apply the Holm post-hoc correction.

Proposed One-Year and Long-Term Outcomes:

One-year outcomes specific to the completion of the project are discussed below in the year-end progress summary section. The long-term outcome for the award included serving as a major part of a foundation for a planned submission of an NIH grant as the PI, advancing my career aspiration to conduct clinical trials, implementing intensive vascular risk factor control, exercise/physical activity programs, and other lifestyle interventions in middle-aged and older cognitively unimpaired individuals. There is a proposal to this end currently being developed, understanding the effect of intensive systolic blood pressure control on white matter hyperintensity volume in middle-aged individuals. This pilot project has advanced this goal in several ways, including but not limited to; providing experience and informing how blood-biomarkers will best fit into the proposal being developed, understanding how vascular risk and at what age ranges it might be likely to influence these biomarkers, informing and providing more experience with conducting analyses at the intersection of AD pathology and vascular risk, and providing collaborative experience other key scientists in this pursuit.

Year End Progress Summary:

Successful completion of the aims has been mixed up to this point though the most important analyses and answering the question posed in Aim 1 is complete. One unanticipated limitation that required alteration of the aims was the lack of plasma sample availability to determine A β 42/40 ratio. The aims were altered to accommodate this limitation and resubmitted as below:

Aim 1. Determine whether the presence of at least one copy (homozygotes and heterozygotes) of APOE4 is associated with abnormal levels of plasma concentrations of NfL and p-tau 217 in both cognitively unimpaired PSEN1 E280A adult mutation carriers and age-matched non-carrier controls.

Aim 2. Determine whether degree of systemic vascular risk, quantified with the Framingham Heart Study cardiovascular disease risk score (FHS-CVD),¹ is associated with abnormal levels of plasma NfL and p-tau 217 in both cognitively unimpaired PSEN1 E280A adult mutation carriers and non-carrier controls.

Aim 3. Examine the interactive effects of the presence of the APOE4 allele with degree of systemic cardiovascular risk on plasma concentrations of NfL and p-tau 217 in both cognitively unimpaired PSEN1 E280A adult mutation carriers and non-carrier controls.

Analyses are complete for revised aim 1. We found that carriage of the APOE4 allele influenced plasma NfL levels in PSEN1 E280A mutation carriers, being associated with higher concentrations of NfL, as was hypothesized. Plasma NfL concentrations begin to differentiate those who are APOE4 carriers from non-carriers at age 47.4, between the median age of onset of MCI and dementia in the kindred.²³ We did not find a similar relationship in mutation carriers for p-tau 217. The trend in the data however was similar to that of NfL, in the anticipated direction and group, with plasma p-tau 217 increasing sooner in APOE4 carriers compared to non-carriers. These results did not reach the threshold for statistical significance but should be the subject of future investigation. We believe it is likely a lack of power and the many younger individuals (less than 30 years of age) included in analyses that lead interesting yet non-significant results. We did not find significant differences between APOE4 carriers and non-carriers in plasma concentrations of those without the PSEN1 E280A mutation. Again, we found intriguing trends in the hypothesized direction, with those carrying the APOE4 allele having a steeper increase in both biomarkers at the higher end of the age range. This suggests once more that it is possible that lack of power and having many participants being much younger than anticipated symptom onset for ADAD especially sporadic AD, resulted in interesting trends but non-significant results. These findings were submitted and accepted for a virtual oral presentation at AAIC 2022.

Aims 2 and 3 are related and analyses currently in process but not yet completed. We experienced significant delay in obtaining all the data we needed, specifically connecting APOE4 genotypes to the ages at which the plasma samples were collected. These analyses are in progress currently however, with an FHS-CVD score calculated for participants but the analysis looking for influence on plasma biomarkers or interaction with APOE4 yet to be conducted. When all analyses are conducted, publication of the findings will be pursued.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Clinicopathological Correlates of Rapidly Progressive Alzheimer's Disease. Robert Alexander, MD, Tom Beach, MD, PhD, Alireza Altri, MD, Kewei Chen, PhD. Banner Alzheimer's Institute; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

The specific aim of this project is to investigate the prevalence, clinical profiles, and already characterized neuropathological assessments of rapidly progressive Alzheimer's Disease (AD) patients using data from the Brain Body Donation Program (BBDP).

Background and Significance:

Rapidly progressive Alzheimer's disease (rpAD) is putative subtype of AD characterized by rapidly progressive cognitive decline and/or short disease duration. Although a consensus definition of rpAD has not been established, these patients have been variously defined in terms of a MMSE score point decrease of >3 points/6 months or >5 points/year. Depending on the definition, it estimated that 10% to 30% of AD cases are rpAD. Recently, an imbalance of rpAD patients across the treatment arms of the aducanumab Phase III study 301 was proposed as a reason for the negative trial result. rpAD is a frequent alternative diagnosis among patients referred to the evaluation of possible Creutzfeld-Jakob Disease (CJD). At present, little is known about the clinical manifestations, genetic factors, CSF and/or plasma biomarker characteristics, or post-mortem findings associated with rpAD. While the early appearance of motor signs and/or psychotic symptoms have been suggested to associated with rpAD, no generally agreed prognostic signs have been established. In addition, whether rpAD is a true subtype of AD or the results of comorbidity with other CNS pathologies is not known. Better characterization and understanding of rpAD could contribute to both clinical practice and clinical trial design.

Preliminary Data, Experimental Design and Methods:

A recent publication using BBDP data from 315 subjects with dementia found annualized mean MMSE decline rates that ranged between 1.48 and 2.16 (Malek-Ahmadi et al, 2019). Cognitive and matching neuropathological data from NACC is available for more than 2,000 subjects and has recently been used in a publication by Beach and Malek-Ahmadi (2021).

Using data from the BBDP, we will explore various operational definitions of rpAD to better understand the patterns of short-term rapid decline in the context of the entire disease course, i.e. are there distinct profiles among rpAD patients, and the prevalence of different rpAD definitions. This will be followed by a comprehensive assessment of clinical and biomarker assessments to identify those variables that may distinguish rpAD from age and gender matched controls with "typical" AD. Finally, rpAD and matched control patients will be compared using pathology categories for AD-specific lesions, comorbid neurodegenerative conditions and comorbid cerebrovascular conditions.

Proposed One-Year and Long-Term Outcomes:

All analyses will be completed with one year. The findings will be communicated to the scientific community via a publication and/or presentation at a scientific meeting. This study will contribute to a more general goal of delineating clinical trajectories of neuropathologically defined groups using advanced modeling techniques and will contribute to the ongoing build of clinical research infrastructure and internal expertise within BAI.

Year End Progress Summary:

During the 2020-21 funding period, we identified 731 subjects in the BBDP who had received a diagnosis of dementia during life and had evidence of NIA-Reagan intermediate or high neuropathologic changes at autopsy. 600 of these subjects had a least 2 MMSEs and were included in the initial analysis. We calculated the annual rate of change for this group, and 271 had an annualized increase of ≥ 3 points/ year and 229 had a rate of <3 points/year. In order to improve the robustness of the MMSE data, we further filtered this group to only include subjects that where at least 2 MMSEs were > 3 months apart and the initial MMSE score was >20 . In addition, we excluded subjects whose last MMSE assessments were more than 2 years before death. This yielded a group of 585 subjects with a mean annualized rate of decline of -2.5 points/year (SD 2.3). We further divided this group into 5 categories, annualized decline of > 1 point/year (n=10), between 1 and -2 points/year (n=265), < -2 to -5 points/year (n=225), < -5 to -10 points/year (n=79), and < -10 points/year (n=6).

We then analyzed the relationship between the annualized rate of decline and the following demographic, clinical, and neuropathologic variables:

Demographic (gender; years of education; age at death; time from last MMSE to death)

Clinical (diagnosis, including AD, PD, MSA, Dementia with Lewy Bodies, Vascular Dementia, Progressive Supranuclear Palsy, Hippocampal Sclerosis, Corticobasal Degeneration, Pick's Disease; age at dementia diagnosis; age at neurologic diagnosis; years since dementia diagnosis; years since neurologic diagnosis; ApoE genotype; AVLT testing results; Unified Parkinson's Disease Rating Score, Part 3 (Motor) results; Trails A and Trails B results; COWA results; Animal Fluency results; Clinical Dementia Rating results (global score and sum of boxes); Geriatric Depression Scale results; NPI results)

Neuropathologic (postmortem interval; brain weight; Braak score; plaque density; NIA Reagan score; plaque total; neurofibrillary tangle total; cerebral amyloid angiopathy score; white matter score; Lewy Body score; Lewy Body stage; FTLT-TDP (yes/no); TDP43 (yes/no); Argrophilic grains (yes/no); cerebral amyloid angiopathy (yes/no); DLB probability; Huntington's Disease (yes/no); PD (yes/no); MSA (yes/no); Pick's Disease (yes/no).

For this hypothesis establishing study, our analyses were all of an exploratory nature. Thus, we did not correct for multiple comparisons. Nominal statistical significance was set at $p=0.05$ for two-tailed test. First, combining the subjects from all the five groups with different decline rates (i.e., over all subjects), we explored the overall relationship of the annualized rate of decline with each of the variables listed above using the non-parametric rank-order association using Kendal tau-b test and not correcting for multiple comparisons. Secondly, we investigated the variation of each demographic, clinical, and neuropathological measure among the five groups with different decline rates. If a given measure was continuous (with age as an example), we used the non-parametric Kruskal-Wallis test, the counterpart of the parametric one-way ANOVA. If a given measure was categorical (such as sex) with less than or equal to six categories, we used the Chi-square test for [distributional] proportion differences. Additional Cochran–Armitage test for trend proportions was also performed. All statistical analyses were carried out using Statistical toolbox and our own codes in MATLAB

With exception of Lewy Body score (Chi-square test, $p=0.016$), we did not identify any demographic, clinical or neuropathologic variable that was correlated with the annualized rate of decline on MMSE. To account for "pathologic load" we then divided neuropathologic variables

such as Braak score, plaque count or neurofibrillary tangle total, by years of illness, but this also did not need yield any significant correlations.

Although the results from the available BBDP data did not identify the key driver(s) of the rate of cognitive decline in AD subjects, examination of the results revealed some consistent trending contributions from multiple demographics, clinical and neuropathological measures. Thus, we believe the proper integration of information over all the measures may provide a means to 'predict' the decline, though each measure does not have enough power to do so. Following this logic, we further explored various machine learning (ML) techniques especially artificial neural network (ANN) as a way to combine the information from all measures to collectively assess the rate of decline. For this purpose, we randomly divide the entire dataset as 70%, 15% and 15% as training, validation and testing sub-datasets. Using a single hidden-layer ANN for simplicity and interpretability, we used neuropathological surrogates of imaging or fluid biomarkers in addition to demographic variables and were able to account for 37% variation of the decline rate ($R^2=0.370$) based on the testing dataset ($p=5.12e-07$). Potential next steps would be to use actual imaging and fluid biomarker correlates of these neuropathological measures in models to assess how well they could serve as screening tools for those predicted to have rpAD in clinical trials.

Reference List:

1. Abu-Rumeileh S, Capellari S, Parchi P. Rapidly Progressive Alzheimer's Disease: Contributions to Clinical-Pathological Definition and Diagnosis. *J Alzheimers Dis.* 2018;63(3):887-97. doi: 10.3233/JAD-171181. PubMed PMID: 29710713.
2. Schmidt C, Wolff M, Weitz M, Bartlau T, Korth C, Zerr I. Rapidly progressive Alzheimer disease. *Arch Neurol.* 2011;68(9):1124-30. doi: 10.1001/archneurol.2011.189. PubMed PMID: 21911694.
3. Malek-Ahmadi M, Beach TG, Zamrini E, Adler CH, Sabbagh MN, Shill HA, Jacobson SA, Belden CM, Caselli RJ, Woodruff BK, Rapsack SZ, Ahern GL, Shi J, Caviness JN, Driver-Dunckley E, Mehta SH, Shprecher DR, Spann BM, Tariot P, Davis KJ, Long KE, Nicholson LR, Intorcchia A, Glass MJ, Walker JE, Callan M, Curry J, Cutler B, Oliver J, Arce R, Walker DG, Lue LF, Serrano GE, Sue LI, Chen K, Reiman EM. Faster cognitive decline in dementia due to Alzheimer disease with clinically undiagnosed Lewy body disease. *PLoS One.* 2019;14(6):e0217566. doi: 10.1371/journal.pone.0217566. PubMed PMID: 31237877; PMCID: PMC6592515
4. Beach TG, Malek-Ahmadi M. Alzheimer's Disease Neuropathological Comorbidities are Common in the Younger-Old. *J Alzheimers Dis.* 2021;79(1):389-400. doi: 10.3233/JAD-201213. PubMed PMID: 33285640; PMCID: PMC8034496.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Alzheimer's Prevention Initiative. Eric M. Reiman, MD, Pierre N. Tariot, MD, Jessica B. Langbaum, PhD, Robert Alexander, MD. Banner Alzheimer's Institute; University of Arizona; Arizona State University; Arizona Alzheimer's Consortium.

Specific Aims:

1. To continue to conduct 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 baseline trial data, prepare for end of trial data and sample sharing.
2. To support efforts to analyze data and samples from the recently discontinued API Generation Study 1 and Generation Study 2 trials.
3. To support efforts to share data and samples from the recently discontinued API Generation Study 1 and Generation Study 2 trials with the scientific community.
4. To plan and secure funding for other preclinical treatment trials programs/surrogate marker development programs in cognitively unimpaired individuals who are at risk for ADAD or LOAD (e.g., our proposed API A4 gantenerumab prevention trial).
5. To continue to support registries designed to assist with participant recruitment.

Background and Significance:

The Alzheimer's Prevention Initiative (API) was established to help advance this new era in Alzheimer's prevention research¹. It includes several complementary preclinical treatment trial programs/surrogate marker development programs in cognitively normal individuals who (1) are autosomal dominant AD (ADAD) mutation carriers ages 30-60 (API ADAD Trial; NCT01998841)², (2) are apolipoprotein E (APOE) ϵ 4 homozygotes ages 60-75 (API Generation Study 1; NCT02565511), (3) are APOE carriers (homozygotes and heterozygotes, heterozygotes must have elevated brain amyloid) ages 60-75 (API Generation Study 2; NCT03131453)³, (4) have elevated brain amyloid (our proposed API A4 prevention trial). It also includes the Alzheimer's Prevention Registry to help inform stakeholders and support their enrollment in these and other prevention trials⁴, GeneMatch to help identify and support the enrollment of APOE4 homozygotes, heterozygotes and non-carriers in prevention trials⁵, programs to disclose and assess the impact of a person's genetic or biomarker risk⁶, future prevention trials (TBD), and other efforts to find and support the approval and availability of AD prevention therapies. Non-overlapping state and institutional funds are used to support these and related efforts, complement our NIH, philanthropic, and industry support, and help to find and support the approval of a prevention therapy as soon as possible.

Preliminary Data:

We and our colleagues from the University of Antioquia have reported cross-sectional evidence of biomarker changes in cognitively healthy PSEN1 E280A mutation carriers compared to kindred non-carriers^{7,8} and are currently exploring the longitudinal trajectory of these biomarkers. We demonstrated an association between two copies of the rare APOE3 Christchurch variant in a PSEN1 E280A mutation carrier who was resistant to the clinical onset of ADAD and performed of related experimental studies to suggest the mechanism by which APOE, its variants and future APOE-related treatments might exert their therapeutic effects⁹. We demonstrated that two copies of the APOE2 allele are also associated with an exceptionally low risk of neuropathologically confirmed AD dementia, found that APOE and its common variants have a greater impact on AD dementia risk than previously thought, provided further support for the development of APOE-

modifying drug and gene therapies in a case-control study of >5,000 well characterized brain donors¹⁰. We and our colleagues demonstrated the promise of plasma p-tau217 in the diagnosis and unusually early detection of AD, including the onset of measurements p-tau217 elevations about two decades before the ADAD mutation carriers' estimated age at MCI onset¹¹. We have published manuscripts describing the API ADAD trial², baseline characteristics of trial participants¹², the API Generation Program³, the Generation Program risk disclosure process⁶, the Alzheimer's Prevention Registry⁴ and its GeneMatch program⁵. We continue to refine and establish the clinical meaningfulness of our API preclinical ADAD composite cognitive test score¹³ and API composite cognitive test score (APCC)^{14,15}.

Experimental Designs and Methods:

To accomplish these overall goals and Aim 1, we will continue to follow participant randomized into the API ADAD trial until the last participant enrolled completes 5 years of blinded treatment (a "common close" design), continue to collect tau PET, plan for disclosure of ADAD mutation carrier status at the appropriate time after the trial is completed in those who wish to learn this information, and analyze and share baseline data. For Aim 2, we will work with our Novartis and academic colleagues to analyze data and samples from the Generation Program. For Aim 3, we will continue to work with our Novartis colleagues to implement a data and sample sharing program, following the "Collaboration for Alzheimer's Prevention" (CAP) data and sample sharing principles. To accomplish Aim 4, we will continue to work with our A4 and Roche colleagues to develop plans for a prevention trial with gantenerumab, aiming to begin enrollment by end of 2021. In addition, API leadership will continue conversations with other pharma companies regarding other potential prevention trials. To accomplish Aim 5, we will continue to expand the API Colombia Registry, for PSEN1 E280A kindred members, the web-based Alzheimer's Prevention Registry, and its GeneMatch program.

Proposed One-Year and Long-Term Outcomes:

For Aim 1, we will continue to work with our colleagues at Roche to expand the baseline data sharing program to include additional variables. For Aim 2, Banner will work with Novartis and Amgen to analyze trial data and samples and prepare manuscripts for publication. For Aim 3, Banner will work with data and sample sharing programs such as LONI and NCRAD to share all trial data and samples with the scientific community following CAP principles. For Aim 4, we will work with our colleagues from A4 and Roche to finalize the trial protocol and operational details to meet our goal of beginning trial enrollment by end of 2021. The API will continue to seek additional external, non-state funding from NIH, industry, and philanthropic organizations to support our efforts to conduct trials in at-risk populations.

Year End Progress Summary:

Aim 1 (API ADAD Trial). With primary support from initial and subsequent NIA grants, philanthropy, Genentech and its parent organization Roche, the API ADAD continued to meet its stated goals. 365 participants were screened, 252 participants (including 162 PSEN1 E280A mutation carriers) were enrolled, with the last participant enrolled in early 2017. Topline results were shared in June 2022 and initial clinical and biomarker results will be presented at the Alzheimer's Association International Conference on August 2, 2022. Topline results indicated that trial did not demonstrate a statistically significant clinical benefit in either of its co-primary endpoints assessing the rate of change in cognitive abilities or episodic memory function, measured by the Alzheimer's Prevention Initiative (API) ADAD Composite Cognitive Test Score and the Free and Cued Selective Reminding Test (FCSRT) Cueing Index, respectively. Small numerical differences favoring crenezumab over placebo were observed across the co-primary

and multiple secondary and exploratory endpoints, but they were not statistically significant. In accordance with Collaboration for Alzheimer's Prevention (CAP) principles¹⁶ we and industry partners have developed mechanisms to share baseline trial data and analyses with the field in ways that protect research participant anonymity, confidentiality and genetic risk disclosure and clinical trial integrity, and we have an agreement to provide a public resource of trial data and biological samples after the trial is over. A manuscript describing the API ADAD Trial data and sample sharing program is currently under review.

Aim 2 (API Generation Program Data & Sample Analyses). The Alzheimer Prevention Initiative (API) Generation Program evaluated the effectiveness of the BACE1 inhibitor, umibecestat, and the active immunotherapy, CAD106, in delaying the onset of AD symptoms in APOE4 carriers (16). The Generation Program included two studies implemented in 23 countries at 207 sites. Recruitment in the program and treatment with umibecestat was terminated in July 2019 after detecting an early signal of mild worsening in some measures of cognitive function with umibecestat. At the time of discontinuation, 9623 participants had been recruited, more than 2700 completed the 12-week screening phase with amyloid (PET or CSF) testing; approximately 27% were APOE4 homozygotes (HM). About 60% of HMs and 35% of heterozygotes (HTs) had elevated brain amyloid. A total of 1623 participants were randomized: 478 to Generation Study 1 (all HMs) and 1145 to Generation Study 2 (20% HMs and 80% HTs with elevated amyloid). The last participant last visit occurred in Q2 2020 after which database lock occurred. Several manuscripts describing the available data and samples are currently being prepared for submission to journals for peer review.

Aim 3 (API Generation Program Data & Sample Sharing). Considerable effort has occurred (and is still underway) to transfer biological samples to the National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD) and all the clinical and brain imaging data to the Laboratory for NeuroImaging (LONI) for sharing with the scientific community. We anticipate data and samples will be available for researchers in Q3 2022. In addition, efforts are underway to make the Generation Program trial data available via the Alzheimer's Disease Data Initiative (ADDI).

Aim 4 (Other Prevention Trials). In 2018, API and A4 leaders received a \$33M NIA grant to help support a proposed prevention trial of an A β -plaque antibody in cognitively unimpaired A β + adults. Although we originally intended to partner with Biogen and use aducanumab, in March 2019, Biogen announced the discontinuation of their two Phase 3 trials (ENGAGE and EMERGE) of aducanumab in patients with MCI due to AD and mild AD dementia. As a result, the API and A4 leaders entered discussions with another industry partner (Roche) and are planning for a prevention trial of a different A β -plaque antibody (gantenerumab) in cognitively unimpaired A β + adults (the SKYLINE trial). We have received NIA approval to change the aims of the original grant to focus primarily on the initial support provided to aid in the design of the SKYLINE trial, to support two ancillary studies in a subset of US-based SKYLINE participants and prepare for baseline trial data and sample sharing. Efforts are also underway to launch new preclinical treatment trials programs/surrogate marker development programs in cognitively unimpaired individuals who are at risk for ADAD or LOAD.

Aim 5 (Recruitment Registries). We continue to expand the Alzheimer's Prevention Registry (APR), a web-based registry focused on encouraging enrollment into prevention studies. The Registry has >380,000 enrollees and is actively recruiting for studies locally and nationally⁴. In November 2015, the Registry launched its GeneMatch program which collects genetic samples from participants for APOE genotyping and uses the genetic results in part to help match people

to research studies⁵. More than 100,000 have joined GeneMatch to date. In August 2021 we were awarded an R33 (R33AG070604-01A1) to optimize the research infrastructure of the Registry (including GeneMatch). The R33 will incorporate data and learning from our R01 to increase diversity of registry enrollees (R01AG063954).

References:

- 1 Reiman, E. M., Langbaum, J. B. S. & Tariot, P. N. Alzheimer's Prevention Initiative: a proposal to evaluate presymptomatic treatments as quickly as possible. *Biomarkers in Medicine* **4**, 3-14 (2010).
- 2 Tariot, P. N. *et al.* The Alzheimer's Prevention Initiative Autosomal-Dominant Alzheimer's Disease Trial: A study of crenezumab versus placebo in preclinical PSEN1 E280A mutation carriers to evaluate efficacy and safety in the treatment of autosomal-dominant Alzheimer's disease, including a placebo-treated noncarrier cohort. *Alzheimers Dement (N. Y.)* **4**, 150-160, doi:10.1016/j.trci.2018.02.002 [doi];S2352-8737(18)30005-2 [pii] (2018).
- 3 Lopez, L. C. *et al.* The Alzheimer's Prevention Initiative Generation Program: Study design of two randomized controlled trials for individuals at risk for clinical onset of Alzheimer's disease. *Alzheimers Dement (N. Y.)* **5**, 216-227, doi:10.1016/j.trci.2019.02.005 [doi];S2352-8737(19)30008-3 [pii] (2019).
- 4 Langbaum, J. B. *et al.* The Alzheimer's Prevention Registry: a large internet-based participant recruitment registry to accelerate referrals to Alzheimer's-focused studies. *J Prev Alz Dis* **7**, 242-250, doi:10.14283/jpad.2020.31 (2020).
- 5 Langbaum, J. B. *et al.* GeneMatch: a novel recruitment registry using at-home APOE genotyping to enhance referrals to Alzheimer's prevention studies. *Alzheimer's and Dementia* **15**, 515-524, doi:<https://doi.org/10.1016/j.jalz.2018.12.007> (2019).
- 6 Langlois, C. M. *et al.* Alzheimer's Prevention Initiative Generation Program: Development of an APOE genetic counseling and disclosure process in the context of clinical trials. *Alzheimers Dement (N. Y.)* **5**, 705-716, doi:10.1016/j.trci.2019.09.013 [doi];S2352-8737(19)30074-5 [pii] (2019).
- 7 Fleisher, A. S. *et al.* Associations Between Biomarkers and Age in the Presenilin 1 E280A Autosomal Dominant Alzheimer Disease Kindred: A Cross-sectional Study. *JAMA Neurol* **72**, 316-324, doi:2089217 [pii];10.1001/jamaneurol.2014.3314 [doi] (2015).
- 8 Fleisher, A. S. *et al.* Florbetapir PET analysis of amyloid- β deposition in presenilin 1 E280A autosomal-dominant Alzheimer's disease kindred: a cross-sectional study. *Lancet Neurol* **11**, 1057-1065, doi:10.1016/S1474-4422(12)70227-2 (2012).
- 9 Arboleda-Velasquez, J. F. *et al.* Resistance to autosomal dominant Alzheimer's disease in an APOE3 Christchurch homozygote: a case report. *Nat. Med* **25**, 1680-1683, doi:10.1038/s41591-019-0611-3 [doi];10.1038/s41591-019-0611-3 [pii] (2019).
- 10 Reiman, E. M. *et al.* Exceptionally low likelihood of Alzheimer's dementia in APOE2 homozygotes from a 5,000-person neuropathological study. *Nat. Commun* **11**, 667, doi:10.1038/s41467-019-14279-8 [doi];10.1038/s41467-019-14279-8 [pii] (2020).
- 11 Palmqvist, S. *et al.* Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders. *JAMA* **324**, 772-781, doi:2768841 [pii];10.1001/jama.2020.12134 [doi] (2020).
- 12 Rios-Romenets, S. *et al.* Baseline demographic, clinical, and cognitive characteristics of the Alzheimer's Prevention Initiative (API) Autosomal-Dominant Alzheimer's Disease Colombia Trial. *Alzheimers Dement* **16**, 1023-1030, doi:10.1002/alz.12109 [doi] (2020).
- 13 Ayutyanont, N. *et al.* The Alzheimer's Prevention Initiative composite cognitive test score: sample size estimates for the evaluation of preclinical Alzheimer's disease treatments in

- presenilin 1 E280A mutation carriers. *J Clin. Psychiatry* **75**, 652-660, doi:doi:10.4088/JCP.13m08927 (2014).
- 14 Langbaum, J. B. *et al.* The Alzheimer's Prevention Initiative Composite Cognitive Test: a practical measure for tracking cognitive decline in preclinical Alzheimer's disease. *Alzheimers Res. Ther* **12**, 66, doi:10.1186/s13195-020-00633-2 [doi];10.1186/s13195-020-00633-2 [pii] (2020).
- 15 Graf, A. *et al.* Assessment of Clinical Meaningfulness of Endpoints in the Generation Program by the Insights to Model Alzheimer's Progression in Real Life (iMAP) Study. *J Prev Alzheimers Dis* **6**, 85-89, doi:10.14283/jpad.2018.49 [doi] (2019).
- 16 Weninger, S. *et al.* Collaboration for Alzheimer's Prevention: Principles to guide data and sample sharing in preclinical Alzheimer's disease trials. *Alzheimer's & Dementia* **12**, 631-632, doi:<http://dx.doi.org/10.1016/j.jalz.2016.04.001> (2016).

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Statistical and Neuroimaging Data Science Core Resources Serving the Consortium Members. K Chen, Y Su, H Protas, M Malek-Ahmadi, Y Chen, J Luo, W Lee, V Ghisays, G Alexander, R Chang, K Devick, B Readhead, I Piras, D Saner, EM Reiman. Banner Alzheimer's Institute; Arizona State University; University of Arizona; Mayo Clinic; Arizona Alzheimer's Consortium; Translational Genomics Research Institute

Specific Aims:

- 1) To organize and share imaging data and imaging-based measurements using state-of-the-art methodologies for multiple large datasets from Arizona APOE study, the Arizona ADRC, ADNI and other projects;
- 2) To offer comprehensive statistical and image analysis services to investigators inside and outside Arizona based on the common interest and their needs.

Background and Significance:

With the joint efforts from the investigators in our Consortium, in Arizona and those outside Arizona, the comprehensive datasets of imaging, fluid biomarkers, cognitive, and clinical measurements from multiple projects enhanced our understanding of the underlying mechanisms that lead to neurodegenerative changes, cognitive decline and dementia. A major local effort is our APOE e4 study with more than 1500/2100 MRI/PET scans from 400+ cognitively unimpaired individuals. Our new NIH supported APOE2.0 study investigates 6-level AD risks related to the carriage of APOE e2, 3 or 4 gene doses. Another effort is led by Arizona ADRC with biomarker, neuropathology and other cores aimed to acquire imaging, fluid biomarker, cognitive and clinical data from ADRC and Brain and Body Donation Program participants. Data from these projects and from ADNI, ADNI-DOD, and some early phase trials among others have been used to inform our prevention trials design. Also, we provided high quality data services to these projects.

Over the years, the Computational Image Analysis Lab (CIAL) has continued, in working and supporting ADRC DMSC, to serve as a core resource of imaging and statistical expertise to facilitate AD research by collaborating with local, national, and international investigators. With state funding support through the Arizona Alzheimer's Consortium, our lab has helped collaborating investigators perform imaging and statistical analysis using state-of-the-art methodologies developed by our lab and elsewhere. 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 be impossible (1-17). 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 if funded. We would like to continue this effort supporting the research advancements of our Consortium investigators and those inside and outside Arizona with common research interests.

Preliminary Data:

We have assembled a database of 4312 T1w-MRI, 1309 PIB, 3393 FBP, 924 FTP, and 5453 FDG scans with quantitative measurements. In addition, a comprehensive database for 834 historical and active Arizona APOE participants from 3569 visits were also compiled with 57 variables including demographic information, cognitive and clinical assessments, imaging biomarkers, CSF, and plasma biomarkers. These data are across Arizona APOE, ADRC, ADNI and OASIS, and are available to share with AAC investigators and the broad research community. We introduced Deep Learning modeling and Machine Learning techniques to improve the harmonization of amyloid measurements using PiB or florbetapir PET tracers. This effort will facilitate comparison of analysis results from different centers and groups (18-20).

CIAL also continue to perform collaborative research both within and outside of the Consortium. We provided data and image analysis for Dr. Braden (ASU) for her K-ward on the study of autism and we are in the process of assisting her subsequent R01 application. We worked closely with Dr. Yalin Wang (ASU) for his two grant applications. Working with Drs. Qi Wang and Ben Readhead on multi-omics data analysis, we also contributed to two AAIC abstracts and journal articles (21). We started to regularly participate in research meetings and provide our statistical advice to Drs. Alireza Atri and Thomas Beach at Banner Sun Health Research Institute. We started our statistical and imaging analysis assistance to Dr. Gwenn Smith, John Hopkins, on her depression study. Using multi-modal partial least square (MMPLS), we characterized the covarying pattern between serotonin transporter and beta amyloid deposition in people with late-life depression. We subsequently joined her for an RO1 application. Using MMPLS and collaborating with Dr. Yakeel Guiroz, MGH for co-analyzing her PiB amyloid PET and task functional MRI data. We also used our statistical region of interest method for Dr. Longo, Stanford study on cerebral glucose metabolism. Additionally, we analyzed amyloid PET data from ADNI-DOD project. Using Monte-Carlo simulation for assessing overall global statistical significance, we found that those PTSD veterans with the use of SRI antidepressants had lower amyloid burden than those PTSD veterans without. Recently, we started our planning to work with Dr. Yu (ASU) for her non-pharmaceutical intervention studies. In addition, our team also is working on novel blood-based biomarkers and helped other investigators on their grant applications (Drs. Schaefer, Berisha, Hahn, Pruzin and Lee-Iannotti).

Experimental Designs and Methods:

Aim 1. We will continue our efforts to organize and share high-quality imaging derived measurements from the Arizona APOE cohort, ADRC, ADNI and OASIS-3 to Consortium investigators. These derived imaging measures will be integrated into our database together with the clinical, neuropsychological, fluid biomarkers and behavior measures. Neuroimaging derived measures based on novel methods we developed will be added over time with careful cross-validation.

Aim 2. We will continue our effort to provide imaging and statistical services in working and supporting ADRC DMSC. Identified projects include:

- a) Dr. Richard Caselli (Mayo), the analysis of longitudinal Arizona APOE data to identify early predictors of cognitive decline;
- b) Dr. Blair Braden (ASU) and her PhD student K01 training awards, and R01 grant proposal;
- c) Dr. Sydney Schaefer (ASU), her development of novel motor tasks in AD research and her R01 grant application;
- d) Dr. Jiah Yoo (UA), statistical support for missing data handling of her NIH grant application;
- e) Drs. Thomas Beach and Alireza Atri (BSHRI), statistical support to their research;
- f) Drs. Berisha and Hahn (ASU), their Causality modeling research with our neuroimaging expertise;
- g) Dr. Yalin Wang (ASU), his R21/R01 grant/applications and collaboration on advanced imaging methods;
- h) Dr. Qi Wang (ASU), her multi-omics investigation of AD;
- i) Dr. Fang Yu (ASU), using neuroimaging measures in her non-pharmaceutical intervention studies;
- j) Dr. Smith (John Hopkins), our MMPLS analysis for her late-life depression study including new MCI and longitudinal data;
- k) Dr. Weiner (UCSF), his study of SRI antidepressants effects on amyloid burden in veteran with PTSD from the ADNI-DOD project;

- l) Dr. Longo (Stanford), FDG-PET and T1 MRI data analysis for his intervention study in patients with mild to moderate AD

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 Arizona APOE, ADRC BI-FB core, ADNI, ADNI-DOD, and OASIS cohorts 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 the fiscal year 2021 to 2022, CIAL worked closely with the DMSC to serve as a core resource for the consortium and local, national, and international investigators. We extended our efforts to generate and curate imaging derived measurements. For the Arizona APOE cohort, in addition to what has been collected in the previous year, 139 FreeSurfer sessions, 148 FDG PUP sessions, 45 FTP PUP sessions, 25 PIB PUP sessions were obtained. For the ADNI cohort, 576 FreeSurfer sessions, 197 FBP PUP sessions, 117 FTP PUP sessions, SPM analysis of 118 FBP scans and 545 FDG scans were curated in the past year. We also collected 128 FreeSurfer sessions, 39 FBP PUP sessions, 85 PIB PUP sessions, and 119 FTP PUP sessions from the BIFB cohort. The summary datasheet with newly added data is compiled with the same 57 variables including basic demographic information, cognitive and clinical assessments, imaging biomarkers, CSF and plasma biomarkers. This data has been shared with several AAC investigators and is available to the broad research community upon request.

For our continued efforts on harmonization of amyloid PET measurements from different tracers and processing pipelines. We are very pleased to report that we have one publication on using the Residual Inception Encoder-Decoder Neural Network demonstrating significant improvements in the harmonization of entire brain images (i.e., at the voxel and whole brain level) than established methods (22). An ROI-based artificial neural network (ANN) approach involving 7/6 neurons in the 1st/2nd hidden layers improved r from 0.904 to 0.987 ($p \leq 8.3e-12$). In the independent test set, this ANN improved r to 0.981 from 0.927 ($p \leq 6.6e-4$). Findings were presented last year (Chen, AAIC 2021) and a manuscript is now in preparation.

With the State support in conjunction with our newly received our ADRC grant award, we continued systematically updating several major standard image analysis pipelines. The updates allow us to 1) make our pipelines compatible with newest version of SPM and FreeSurfer, and 2) to share our pipelines more easily with researchers inside and outside Arizona. One of these standard pipelines, the multi-modal partial least square (MMPLS) has been shared with several researchers in Arizona and collaborators in other states.

With the State support, our team has been working closely with the ADRC DMSC and Biomarker Core to generate standardized brain imaging measurements and support relevant analyses of these and other biomarker data. Related, we are preparing a manuscript to report our finding that APOE4 non-carriers had higher association of vascular risk with white matter hyperintensity volume than in APOE4 carrier.

We continued to assist investigators in their AD-related grant applications. We assisted Yalin Wang, ASU in the preparation of a funded R21 grant, entitled "Developing a Univariate Neurodegeneration Imaging Biomarker with Optimal Transportation;" we contributed to related publications (23, 24) and manuscripts; and we provided the support needed for his recently submitted R01 grant application "Improving Screening Efficiency and Outcome Sensitivity in Alzheimer's Disease Clinical Trials with Hippocampal Surface Morphometry and Geometric

Machine Learning”. We assisted Sydney Schaefer, ASU in the recent resubmission of an R01 grant application entitled “Using a rapid motor task to enrich clinical trials in Alzheimer’s disease requiring amyloid positivity”, which uses a novel motor task to identify persons with mild cognitive decline. We assisted Blair Braden, ASU in the recent submission of an RO1 grant application, entitled ‘Delineating the Link between Alzheimer’s and Autism: Multi-Level Genomic, Brain, Cognitive, and Comorbidity Approaches’. Kewei Chen and Ben Readhead provided mentorship and support for Qi Wang, a promising ASU investigator, in the analysis of cell-specific omics data from our Brain donor AD cases and controls and brain homogenate data from AMP-AD, and in the analysis of postmortem brain tissues from multiple AD cohorts to identify the transcriptomic signature and gene co-expression networks, resulting in two separate publications (21, 25). With the support, Dr. Wang submitted an R03 grant application in late 2021, entitled ‘Cell-type specific gene regulatory networks in Alzheimer’s disease from pseudo-time series data’. We also provided statistical and neuroimaging assistances to Dr. Jiah Yoo (UA) and Drs. Berisha and Hahn (ASU) for their grant applications. We have also provided statistical support and/or reviews of ADRC-related developmental and pilot project grant applications, and we continue to provide support for a larger number of investigators, fellows, and students in the design of their studies, the analysis of data and the preparation of abstracts, manuscripts, and grants. These include Yakeel Quiroz and her MGH/Harvard colleagues (26-28), Chris Weise and his University of Leipzig colleagues (manuscript in preparation), Dr. Suchy-Dacey from Washington State University and its Native American Research Center for Minority Aging Research (NA-RCMAR), Robert Stern and his colleagues from Boston University (29), Tammy Benzinger, Beau Ances and their colleagues at Washington University, and other young investigators at several of our institutions (e.g., Valentina Ghisays, Jeremy Pruzin, and Willemijn Jansen at BAI and several colleagues at BSHRI).

Related to statistical training and educational opportunities, Michael Malek-Ahmadi initiated a quarterly webinar series for the national ADRC community that focuses on statistical and methodologic approaches. He invites speakers, advertises the webinars through Arizona ADRC and NACC Data Core e-mail distribution lists. This webinar series has garnered significant interest local and national ADRC interest. The first webinar, “Promoting Statistical Rigor in Scientific Manuscripts: Perspectives of a Statistical Reviewer” was held in October 2021. The second webinar was held in January 2022 on sigmoidal mixed-model approaches to cognitive outcome data. The April 2022 webinar will discuss latent constructs of dementia. All webinars are recorded and are uploaded to a YouTube channel that is publicly available. Dr. Malek-Ahmadi has been preparing one-day workshops on the use of R statistical software, which will be in Phoenix and Tucson. He was recently elected as Programs Chair for Design and Data Analytics Professional Interest Area for ISTAART. Drs. Malek-Ahmadi and Chen and other statistics team members provided mentorship and support for students in other education and training programs, including those in the Mentor-Research Block program for undergraduates at Midwestern University, the ASU-Banner Neuroscience Scholars Program, Scholarly Projects at College of Medicine-Phoenix, UA, and for high school student projects related to the use of AI/ML algorithms in the study of AD. One of the high school students mentored by Dr. Chen received a major scientific award for her project.

In addition to the activities above, Dr. Ignazio Piras at TGen provided his statistical support for the analysis of whole genome at RNA sequencing data inside and outside Arizona (30-34). Dr. Gene Alexander generated 11 published or accepted peer-review articles (35-45), and has been involved in multiple NIH supported projects. Dr. Yi Su and CIAL provided support for numerous colleagues, collaborators, and students. Dr. Matt Huentelman made further development of MindCrowd and plays a major role in Carol Barnes’s recent \$60 NIA-sponsored Precision Aging Network using cognitive assessments in an extraordinarily large number of on-line research participants. Blake Langlais at Mayo Clinic Arizona is now providing statistics support following Katrina Devick’s departure.

Bibliography:

1. Feng DD, Chen K, Wen L. Noninvasive Input Function Acquisition and Simultaneous Estimations With Physiological Parameters for PET Quantification: A Brief Review. *IEEE Transactions on Radiation and Plasma Medical Sciences*. 2020;4(6):676-83.
2. Liu X, Chen K, Weidman D, Wu T, Lure F, Li J, Initiative AsDN. A novel transfer learning model for predictive analytics using incomplete multimodality data. *IISE Transactions*. 2020:1-13.
3. Tu Y, Mi L, Zhang W, Zhang H, Zhang J, Fan Y, Goradia D, Chen K, Caselli RJ, Reiman EM. Computing Univariate Neurodegenerative Biomarkers with Volumetric Optimal Transportation: A Pilot Study. *Neuroinformatics*. 2020;18(4):531-48.
4. Chen X, Chen W, Chen T, Yuan Y, Gong C, Chen K, Wang Z, editors. Self-pu: Self boosted and calibrated positive-unlabeled training. *International Conference on Machine Learning*; 2020: PMLR.
5. van Dyck CH, Nygaard HB, Chen K, Donohue MC, Raman R, Rissman RA, Brewer JB, Koeppe RA, Chow TW, Rafii MS, Gessert D, Choi J, Turner RS, Kaye JA, Gale SA, Reiman EM, Aisen PS, Strittmatter SM. Effect of AZD0530 on Cerebral Metabolic Decline in Alzheimer Disease: A Randomized Clinical Trial. *JAMA neurology*. 2019. doi: 10.1001/jamaneurol.2019.2050. PubMed PMID: 31329216; PMCID: PMC6646979.
6. Seo K, Pan R, Lee D, Thiyyagura P, Chen K, Alzheimer's Disease Neuroimaging I. Visualizing Alzheimer's disease progression in low dimensional manifolds. *Heliyon*. 2019;5(8):e02216. doi: 10.1016/j.heliyon.2019.e02216. PubMed PMID: 31406946; PMCID: PMC6684517.
7. Malek-Ahmadi M, Chen K, Perez SE, Mufson EJ. Cerebral Amyloid Angiopathy and Neuritic Plaque Pathology Correlate with Cognitive Decline in Elderly Non-Demented Individuals. *J Alzheimers Dis*. 2019;67(1):411-22. doi: 10.3233/JAD-180765. PubMed PMID: 30594928.
8. Malek-Ahmadi M, Beach TG, Zamrini E, Adler CH, Sabbagh MN, Shill HA, Jacobson SA, Belden CM, Caselli RJ, Woodruff BK, Rapsack SZ, Ahern GL, Shi J, Caviness JN, Driver-Dunckley E, Mehta SH, Shprecher DR, Spann BM, Tariot P, Davis KJ, Long KE, Nicholson LR, Intorcchia A, Glass MJ, Walker JE, Callan M, Curry J, Cutler B, Oliver J, Arce R, Walker DG, Lue LF, Serrano GE, Sue LI, Chen K, Reiman EM. Faster cognitive decline in dementia due to Alzheimer disease with clinically undiagnosed Lewy body disease. *PLoS One*. 2019;14(6):e0217566. doi: 10.1371/journal.pone.0217566. PubMed PMID: 31237877; PMCID: PMC6592515
9. Kuang L, Han X, Chen K, Caselli RJ, Reiman EM, Wang Y, Alzheimer's Disease Neuroimaging I. A concise and persistent feature to study brain resting-state network dynamics: Findings from the Alzheimer's Disease Neuroimaging Initiative. *Hum Brain Mapp*. 2019;40(4):1062-81. doi: 10.1002/hbm.24383. PubMed PMID: 30569583.
10. Jiang H, Lu N, Chen K, Yao L, Li K, Zhang J, Guo X. Predicting Brain Age of Healthy Adults Based on Structural MRI Parcellation Using Convolutional Neural Networks. *Frontiers in neurology*. 2019;10:1346. Epub 2020/01/24. doi: 10.3389/fneur.2019.01346. PubMed PMID: 31969858; PMCID: PMC6960113.
11. Dong Q, Zhang W, Wu J, Li B, Schron EH, McMahon T, Shi J, Gutman BA, Chen K, Baxter LC, Thompson PM, Reiman EM, Caselli RJ, Wang Y. Applying surface-based hippocampal morphometry to study APOE-E4 allele dose effects in cognitively unimpaired subjects. *Neuroimage Clin*. 2019;22:101744. doi: 10.1016/j.nicl.2019.101744. PubMed PMID: 30852398; PMCID: 6411498.
12. Caselli RJ, Langlais BT, Dueck AC, Chen Y, Su Y, Locke DEC, Woodruff BK, Reiman EM. Neuropsychological decline up to 20 years before incident mild cognitive impairment. *Alzheimers Dement*. 2019. doi: 10.1016/j.jalz.2019.09.085. PubMed PMID: 31787561.
13. Stonnington CM, Wu J, Zhang J, Shi J, Bauer Iii RJ, Devadas V, Su Y, Locke DEC, Reiman EM, Caselli RJ, Chen K, Wang Y, Alzheimer's Disease Neuroimaging I. Improved

Prediction of Imminent Progression to Clinically Significant Memory Decline Using Surface Multivariate Morphometry Statistics and Sparse Coding. *J Alzheimers Dis.* 2021. Epub 2021/03/23. doi: 10.3233/JAD-200821. PubMed PMID: 33749642.

14. Remer J, Dean DC, 3rd, Chen K, Reiman RA, Huentelman MJ, Reiman EM, Deoni SCL. Longitudinal white matter and cognitive development in pediatric carriers of the apolipoprotein epsilon4 allele. *Neuroimage.* 2020;222:117243. Epub 2020/08/22. doi: 10.1016/j.neuroimage.2020.117243. PubMed PMID: 32822813; PMCID: PMC7779366.

15. Stonnington CM, Velgos SN, Chen Y, Syed S, Huentelman M, Thiyyagura P, Lee W, Richholt R, Caselli RJ, Locke DEC, Lu B, Reiman EM, Su Y, Chen K. Interaction Between BDNF Val66Met and APOE4 on Biomarkers of Alzheimer's Disease and Cognitive Decline. *J Alzheimers Dis.* 2020;78(2):721-34. doi: 10.3233/JAD-200132. PubMed PMID: 33044176.

16. Alexander GE, Lin L, Yoshimaru ES, Bharadwaj PK, Bergfield KL, Hoang LT, Chawla MK, Chen K, Moeller JR, Barnes CA, Trouard TP. Age-Related Regional Network Covariance of Magnetic Resonance Imaging Gray Matter in the Rat. *Frontiers in aging neuroscience.* 2020;12:267. doi: 10.3389/fnagi.2020.00267. PubMed PMID: 33005147; PMCID: PMC7479213.

17. Tang YY, Fan Y, Lu Q, Tan LH, Tang R, Kaplan RM, Pinho MC, Thomas BP, Chen K, Friston KJ, Reiman EM. Long-Term Physical Exercise and Mindfulness Practice in an Aging Population. *Front Psychol.* 2020;11:358. doi: 10.3389/fpsyg.2020.00358. PubMed PMID: 32300317; PMCID: PMC7142262.

18. Su Y, Flores S, Hornbeck RC, Speidel B, Vlassenko AG, Gordon BA, Koeppe RA, Klunk WE, Xiong C, Morris JC, Benzinger TLS. Utilizing the Centiloid scale in cross-sectional and longitudinal PiB PET studies. *Neuroimage Clin.* 2018;19:406-16. doi: 10.1016/j.nicl.2018.04.022. PubMed PMID: 30035025; PMCID: PMC6051499.

19. Klunk WE, Koeppe RA, Price JC, Benzinger TL, Devous MD, Sr., Jagust WJ, Johnson KA, Mathis CA, Minhas D, Pontecorvo MJ, Rowe CC, Skovronsky DM, Mintun MA. The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET. *Alzheimers Dement.* 2015;11(1):1-15.e1-4. Epub 2014/12/03. doi: 10.1016/j.jalz.2014.07.003. PubMed PMID: 25443857; PMCID: Pmc4300247.

20. Su Y, Flores S, Wang G, Hornbeck RC, Speidel B, Joseph-Mathurin N, Vlassenko AG, Gordon BA, Koeppe RA, Klunk WE, Jack CR, Jr., Farlow MR, Salloway S, Snider BJ, Berman SB, Roberson ED, Brosch J, Jimenez-Velazques I, van Dyck CH, Galasko D, Yuan SH, Jayadev S, Honig LS, Gauthier S, Hsiung GR, Masellis M, Brooks WS, Fulham M, Clarnette R, Masters CL, Wallon D, Hannequin D, Dubois B, Pariente J, Sanchez-Valle R, Mummery C, Ringman JM, Bottlaender M, Klein G, Milosavljevic-Ristic S, McDade E, Xiong C, Morris JC, Bateman RJ, Benzinger TLS. Comparison of Pittsburgh compound B and florbetapir in cross-sectional and longitudinal studies. *Alzheimers Dement (Amst).* 2019;11:180-90. doi: 10.1016/j.dadm.2018.12.008. PubMed PMID: 30847382; PMCID: 6389727.

21. Wang Q, Chen Y, Readhead B, Chen K, Su Y, Reiman EM, Dudley JT. Longitudinal data in peripheral blood confirm that PM20D1 is a quantitative trait locus (QTL) for Alzheimer's disease and implicate its dynamic role in disease progression. *Clin Epigenetics.* 2020;12(1):189. doi: 10.1186/s13148-020-00984-5. PubMed PMID: 33298155; PMCID: PMC7724832.

22. Shah J, Gao F, Li B, Ghisays V, Luo J, Chen Y, Lee W, Zhou Y, Benzinger TLS, Reiman EM, Chen K, Su Y, Wu T. Deep residual inception encoder-decoder network for amyloid PET harmonization. *Alzheimers Dement.* 2022. doi: 10.1002/alz.12564. PubMed PMID: 35142053.

23. Wang G, Dong Q, Wu J, Su Y, Chen K, Su Q, Zhang X, Hao J, Yao T, Liu L, Zhang C, Caselli RJ, Reiman EM, Wang Y. Alzheimer's Disease Neuroimaging I. Developing univariate neurodegeneration biomarkers with low-rank and sparse subspace decomposition. *Med Image Anal.* 2021;67:101877. doi: 10.1016/j.media.2020.101877. PubMed PMID: 33166772; PMCID: PMC7725891.

24. Wang G, Zhou W, Kong D, Qu Z, Ba M, Hao J, Yao T, Dong Q, Su Y, Reiman EM, Caselli RJ, Chen K, Wang Y. Alzheimer's Disease Neuroimaging I. Studying APOE varepsilon4 Allele

- Dose Effects with a Univariate Morphometry Biomarker. *J Alzheimers Dis.* 2022;85(3):1233-50. doi: 10.3233/JAD-215149. PubMed PMID: 34924383.
25. Wang Q, Chen K, Su Y, Reiman EM, Dudley JT, Readhead B. Deep learning-based brain transcriptomic signatures associated with the neuropathological and clinical severity of Alzheimer's disease. *Brain Commun.* 2022;4(1):fcab293. doi: 10.1093/braincomms/fcab293. PubMed PMID: 34993477; PMCID: PMC8728025.
26. Fox-Fuller JT, Artola A, Chen K, Pulsifer M, Ramirez D, Londono N, Aguirre-Acevedo DC, Vila-Castelar C, Baena A, Martinez J, Arboleda-Velasquez JF, Langbaum JB, Tariot PN, Reiman EM, Lopera F, Quiroz YT. Sex Differences in Cognitive Abilities Among Children With the Autosomal Dominant Alzheimer Disease Presenilin 1 E280A Variant From a Colombian Cohort. *JAMA Netw Open.* 2021;4(8):e2121697. doi: 10.1001/jamanetworkopen.2021.21697. PubMed PMID: 34463747; PMCID: PMC8408665.
27. Fox-Fuller JT, Torrico-Teave H, d'Oleire Uquillas F, Chen K, Su Y, Chen Y, Brickhouse M, Sanchez JS, Aguero C, Jacobs HIL, Hampton O, Guzman-Velez E, Vila-Castelar C, Aguirre-Acevedo DC, Baena A, Artola A, Martinez J, Pluim CF, Alvarez S, Ochoa-Escudero M, Reiman EM, Sperling RA, Lopera F, Johnson KA, Dickerson BC, Quiroz YT. Cortical thickness across the lifespan in a Colombian cohort with autosomal-dominant Alzheimer's disease: A cross-sectional study. *Alzheimers Dement (Amst).* 2021;13(1):e12233. doi: 10.1002/dad2.12233. PubMed PMID: 34541287; PMCID: PMC8438687.
28. Ghisays V, Lopera F, Goradia DD, Protas HD, Malek-Ahmadi MH, Chen Y, Devadas V, Luo J, Lee W, Baena A, Bocanegra Y, Guzman-Velez E, Pardilla-Delgado E, Vila-Castelar C, Fox-Fuller JT, Hu N, Clayton D, Thomas RG, Alvarez S, Espinosa A, Acosta-Baena N, Giraldo MM, Rios-Romenets S, Langbaum JB, Chen K, Su Y, Tariot PN, Quiroz YT, Reiman EM, Group AACT. PET evidence of preclinical cerebellar amyloid plaque deposition in autosomal dominant Alzheimer's disease-causing Presenilin-1 E280A mutation carriers. *Neuroimage Clin.* 2021;31:102749. doi: 10.1016/j.nicl.2021.102749. PubMed PMID: 34252876; PMCID: PMC8278433.
29. Stern RA, Adler CH, Chen K, Navitsky M, Luo J, Dodick DW, Alosco ML, Tripodis Y, Goradia DD, Martin B, Mastroeni D, Fritts NG, Jarnagin J, Devous MD, Sr., Mintun MA, Pontecorvo MJ, Shenton ME, Reiman EM. Tau Positron-Emission Tomography in Former National Football League Players. *N Engl J Med.* 2019;380(18):1716-25. doi: 10.1056/NEJMoa1900757. PubMed PMID: 30969506; PMCID: PMC6636818.
30. Piras IS, Huentelman MJ, Pinna F, Paribello P, Solmi M, Murru A, Carpiello B, Manchia M, Zai CC. A review and meta-analysis of gene expression profiles in suicide. *Eur Neuropsychopharmacol.* 2022;56:39-49. doi: 10.1016/j.euroneuro.2021.12.003. PubMed PMID: 34923210.
31. Windsor R, Stewart SD, Talboom J, Lewis C, Naymik M, Piras IS, Keller S, Borjesson DL, Clark G, Khanna C, Huentelman M. Leukocyte and cytokine variables in asymptomatic Pugs at genetic risk of necrotizing meningoencephalitis. *J Vet Intern Med.* 2021;35(6):2846-52. doi: 10.1111/jvim.16293. PubMed PMID: 34687084; PMCID: PMC8692191.
32. Piras IS, Manti F, Costa A, Carone V, Scalese B, Talboom JS, Veronesi C, Tabolacci C, Persico AM, Huentelman MJ, Sacco R, Lintas C. Molecular biomarkers to track clinical improvement following an integrative treatment model in autistic toddlers. *Acta Neuropsychiatr.* 2021;33(5):267-72. doi: 10.1017/neu.2021.12. PubMed PMID: 33928890.
33. Bettencourt C, Miki Y, Piras IS, de Silva R, Foti SC, Talboom JS, Revesz T, Lashley T, Balazs R, Vire E, Warner TT, Huentelman MJ, Holton JL. MOBP and HIP1 in multiple system atrophy: New alpha-synuclein partners in glial cytoplasmic inclusions implicated in the disease pathogenesis. *Neuropathol Appl Neurobiol.* 2021;47(5):640-52. doi: 10.1111/nan.12688. PubMed PMID: 33368549; PMCID: PMC8219819.
34. Dave N, Vural AS, Piras IS, Winslow W, Surendra L, Winstone JK, Beach TG, Huentelman MJ, Velazquez R. Identification of retinoblastoma binding protein 7 (Rbbp7) as a mediator against

- tau acetylation and subsequent neuronal loss in Alzheimer's disease and related tauopathies. *Acta Neuropathol.* 2021;142(2):279-94. doi: 10.1007/s00401-021-02323-1. PubMed PMID: 33978814; PMCID: PMC8270842.
35. Hausman HK, Hardcastle C, Albizu A, Kraft JN, Evangelista ND, Boutzoukas EM, Langer K, O'Shea A, Van Etten EJ, Bharadwaj PK, Song H, Smith SG, Porges E, DeKosky ST, Hishaw GA, Wu S, Marsiske M, Cohen R, Alexander GE, Woods AJ. Cingulo-opercular and frontoparietal control network connectivity and executive functioning in older adults. *Geroscience.* 2021. doi: 10.1007/s11357-021-00503-1. PubMed PMID: 34950997.
36. Furlong MA, Alexander GE, Klimentidis YC, Raichlen DA. Association of Air Pollution and Physical Activity With Brain Volumes. *Neurology.* 2021. doi: 10.1212/WNL.0000000000013031. PubMed PMID: 34880089; PMCID: PMC8793107.
37. Kraft JN, Albizu A, O'Shea A, Hausman HK, Evangelista ND, Boutzoukas E, Hardcastle C, Van Etten EJ, Bharadwaj PK, Song H, Smith SG, DeKosky S, Hishaw GA, Wu S, Marsiske M, Cohen R, Alexander GE, Porges E, Woods AJ. Functional Neural Correlates of a Useful Field of View (UFOV)-Based fMRI Task in Older Adults. *Cereb Cortex.* 2021. doi: 10.1093/cercor/bhab332. PubMed PMID: 34541604.
38. Boutzoukas EM, O'Shea A, Albizu A, Evangelista ND, Hausman HK, Kraft JN, Van Etten EJ, Bharadwaj PK, Smith SG, Song H, Porges EC, Hishaw A, DeKosky ST, Wu SS, Marsiske M, Alexander GE, Cohen R, Woods AJ. Frontal White Matter Hyperintensities and Executive Functioning Performance in Older Adults. *Front Aging Neurosci.* 2021;13:672535. doi: 10.3389/fnagi.2021.672535. PubMed PMID: 34262445; PMCID: PMC8273864.
39. Van Etten EJ, Bharadwaj PK, Hishaw GA, Huentelman MJ, Trouard TP, Grilli MD, Alexander GE. Influence of regional white matter hyperintensity volume and apolipoprotein E epsilon4 status on hippocampal volume in healthy older adults. *Hippocampus.* 2021;31(5):469-80. doi: 10.1002/hipo.23308. PubMed PMID: 33586848.
40. Evangelista ND, O'Shea A, Kraft JN, Hausman HK, Boutzoukas EM, Nissim NR, Albizu A, Hardcastle C, Van Etten EJ, Bharadwaj PK, Smith SG, Song H, Hishaw GA, DeKosky S, Wu S, Porges E, Alexander GE, Marsiske M, Cohen R, Woods AJ. Independent Contributions of Dorsolateral Prefrontal Structure and Function to Working Memory in Healthy Older Adults. *Cereb Cortex.* 2021;31(3):1732-43. doi: 10.1093/cercor/bhaa322. PubMed PMID: 33188384; PMCID: PMC7869098.
41. Glisky EL, Alexander GE, Hou M, Kawa K, Woolverton CB, Zigman EK, Nguyen LA, Haws K, Figueredo AJ, Ryan L. Differences between young and older adults in unity and diversity of executive functions. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn.* 2021;28(6):829-54. doi: 10.1080/13825585.2020.1830936. PubMed PMID: 33028159; PMCID: PMC8026766.
42. Hardcastle C, Hausman HK, Kraft JN, Albizu A, Evangelista ND, Boutzoukas EM, O'Shea A, Langer K, Van Van Etten E, Bharadwaj PK, Song H, Smith SG, Porges E, DeKosky ST, Hishaw GA, Wu SS, Marsiske M, Cohen R, Alexander GE, Woods AJ. Higher-order resting state network association with the useful field of view task in older adults. *Geroscience.* 2022;44(1):131-45. doi: 10.1007/s11357-021-00441-y. PubMed PMID: 34431043; PMCID: PMC8810967.
43. Boutzoukas EM, O'Shea A, Kraft JN, Hardcastle C, Evangelista ND, Hausman HK, Albizu A, Van Etten EJ, Bharadwaj PK, Smith SG, Song H, Porges EC, Hishaw A, DeKosky ST, Wu SS, Marsiske M, Alexander GE, Cohen R, Woods AJ. Higher white matter hyperintensity load adversely affects pre-post proximal cognitive training performance in healthy older adults. *Geroscience.* 2022. doi: 10.1007/s11357-022-00538-y. PubMed PMID: 35278154.
44. Hardcastle C, Hausman HK, Kraft JN, Albizu A, O'Shea A, Boutzoukas EM, Evangelista ND, Langer K, Van Etten EJ, Bharadwaj PK, Song H, Smith SG, Porges E, DeKosky ST, Hishaw GA, Wu SS, Marsiske M, Cohen R, Alexander GE, Woods AJ. Proximal improvement and higher-order resting state network change after multidomain cognitive training intervention in healthy older adults. *Geroscience.* 2022. doi: 10.1007/s11357-022-00535-1. PubMed PMID: 35258771.

45. Parra KL, Alexander GE, Raichlen DA, Klimentidis YC, Furlong MA. Exposure to air pollution and risk of incident dementia in the UK Biobank. *Environ Res.* 2022:112895. doi: 10.1016/j.envres.2022.112895. PubMed PMID: 35149105.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

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. Don Saner, MS, Ricardo Amador, MS, Matthew Huentelman, PhD, Bruce Petersen, BS, Thomas Beach, MD, Richard J. Caselli MD, Eric M. Reiman, MD, David Coon PhD, Dave Parizek, BS. Banner Alzheimer's Institute (BAI); University of Arizona (UA); Arizona State University (ASU); Mayo Clinic Arizona; Banner Sun Health Research Institute (BSHRI); Translational Genomics Research Institute (TGen); Barrow Neurological Institute (BNI); Arizona Alzheimer's Consortium.

Specific Aims:

1. Work with sites and cores to increase adoption of our Online Reports, Data Discovery Tool, IssueTracker to assist in optimizing operations and recruitment and to solicit feedback on how to improve the tools.
2. While data from our APOE program has been deposited on GAIN and linked to our Data Discovery tool, we have yet to get any requests for data/samples, so would like to continue to find new places to link to our DataDiscovery tool to increase general awareness of the data and samples available from our various programs
3. Migrate our existing Tableau reports to PowerBI and begin to incorporate data from newly implemented systems such as Clinical Conductor
4. Adopt Azure DevOps for our Honest Broker program and find ways to incorporate it into other programs to better track, report and give visibility into the group's efforts

Background and Significance:

The Arizona Alzheimer's Consortium has three longitudinal research programs which are internationally recognized for their productivity, impact, and value to researchers inside and outside of Arizona in the scientific fight against AD, 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. In this project, we propose to enhance the work done in the previous year on a centralized robust data management platform to include more real time reporting, include more data sources, optimize the code that extracts data for NACC submissions to include data consistency checks and create a data sharing platform.

Preliminary Data:

During the past year we have further developed our Online Reports, Data Discovery Tool and IssueTracker, however it has been somewhat challenging to drive adoption of the tools with the reduced visit volumes in the past year. We believe the tools will assist with site operations and help monitor recruitment targets in the coming year.

Experimental Designs and Methods:

As we transition back to more in person visits across the consortium sites, we believe there is a great opportunity for the sites to make better use of our reporting tools, which now include the

ability to receive them by email. We also plan work closely with ORE to ensure that our tools are easily found in the new ADRC specific web site that is being developed. With recruitment, especially of Native Americans and Hispanics being a focus in the coming year, we better leverage and develop new reports and metrics to monitor recruitment and look forward to working closely with the ORE core.

In addition to making sure our tools, data and samples are strategically placed on our ADRC website as well as GAAIN, we intend to author abstracts and posters focused on our tools and how they can be leveraged by operations teams at all sites and others focused on the data, samples and derived measures we have from our research programs as well as the extensive Banner EHR data that can be accessed through our Honest Broker process. Having these at the ready for opportunities to present at conferences will be a good way to enhance visibility on the tools and data.

Banner recently decided to migrate its reporting platform from Tableau to Microsoft PowerBI which has the ability to draw data from an extensive array of data sources as well as making them available both within Banner and with our consortium partners through its integration with Azure. We have started re-writing our current Tableau reports in Microsoft PowerBI and anticipate having them completely re-written and made available to the consortium during the coming funding period.

Another tool Banner has recently adopted is Azure Dev Ops which is an agile based project management system which offers a great opportunity to track and report on the group's work. We have already begun adoption of the tool for our Honest Broker process and the work we do for the All of Us project. Once configured for certain processes it enables efficient tracking of project progress and integrates with PowerBI for reporting metrics.

Proposed One-Year and Long-Term Outcomes:

We anticipate that increasing the visibility of our ADRC specific tools will enable consortium sites to optimize operational efficiencies, assist in new recruitment efforts and provide us with an opportunity for feedback to improve tools and reporting. By making people more generally aware of the data from our research programs as well as Banner Health's EHR data there is a greater opportunity for consortium researchers to publish and potentially apply for new grants. With the adoption of Azure Dev Ops within our group, we hope to gain operational efficiencies, visibility and serve as a model for other groups to potentially adopt the tool.

Year End Progress Summary:

During the past funding period we have had significant effort focused on making participants in our Arizona Alzheimer's Consortium (AAC) more aware of the tools, reports and data that are available in our centralized repository at: <https://aactools.org>. We disseminated information regarding our tools through several pathways including 1) presenting two posters at the fall AAC Scientific conference in Tucson in the fall of 2021; 2) Regularly attending and demonstrating our tools at monthly Clinical Research Coordinator (CRC) meetings to increase awareness and also solicit feedback; 3) regularly attending our Diagnostic Consensus Conference (DCC) where we also presented our tools and solicited feedback 4) Regular 1:1 training sessions for CRCs new to the program. We have also worked to refine some of the reports and tools that help support DCC conversations by providing longitudinal data from participant's records. These engagements have led to valuable improvements in our tools as well as increased adoption as the number of logins to our portal increase by 26 during the past year to a total of 69. Significant among these was more granular reporting back to our CRC's based on data from error/alert reports we receive when submitting our consortium data to the National Alzheimer's Coordinating Center (NACC). We also recognized that Principle Investigators felt there were barriers to accessing data from our local consortium and other national repositories such as NCRAD, NIAGADs and NACC, so we

developed a process for assisting PIs in requesting data from our local consortium, and national repositories and we have received favorable responses from PIs that we assist. In cooperation with our consortium partners we have continued to improve on our data transfer metrics, tracked by NACC, with such as Time to Finalization of Uniform Data Set (UDS) packets.

While working with the ORE core we recognized a source of confusion regarding enrollments numbers, especially with respect to Native American and Hispanic which was stemming from a rather lengthy process to get UDS packet finalized. To help alleviate this, we created new fields in our REDCap database that indicate when a visit has occurred along with the participant's Race and Ethnicity. In addition we are now tracking when packets are initially upload to NACC, but not finalized due to errors and reports. We have modified our Site report to reflect these new data points so sites and Investigators can get an accurate count of packets in the "pipeline". We are reviewing our other reports and aim to incorporate these data points as well.

Our Honest Broker program has fully implemented Azure Dev Ops (ADO) which has a formal workflow as well as the ability to generate reports leveraging it's Application Programming Interface (API) through Microsoft Power BI, which we have also transitioned to during this reporting period. The adoption of ADO has permitted our Clinical Trial Senior Managers (CTSMs) who now submit projects into ADO better visibility into the current status of their/PI's projects. It has also enabled us to centralize the documents supporting data requests in ADO eliminating the need to search for them on One Drive. We have met with the team at Banner Health which has constructed centralized reports for senior leadership and we are in the process of making changes to our implementation of ADO in order to be able to include our work efforts into these centralized reports. As with our ADO reports, all of our new metric reports are done in Power BI and we continue make inroads to converting legacy metric reports from Tableau to PowerBI.

The Data Management Team continues track and reconcile biospecimens stored locally as well as those transferred to the National Centralized Repository for Alzheimer's and Related Dementias (NCRAD). There was a single request for biospecimen's during this reporting period to support a study of Native American's / Hispanic participants, but the number of samples was insufficient to power the study. As we increase our enrollment of Native American's and Hispanics we hope to revisit this project in the future. With our new ADRC grant, we now collect biospecimens at each visits and anticipate an increase in demand going forward as we have more extensive, longitudinal data and samples.

While not a part of our specific aims, we do manage imaging data from several protocols and a new program has been formed, the Standardized Centralized Alzheimer's & Related Dementias (SCAN) which has rigorous standards and QA checks for imaging data it aims to collect. We have begun uploading our historical imaging data from our various programs and have a total of: 176 PET and 14 MRI.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Blood-based Biomarkers in the Risk for Alzheimer's Disease. Gene Alexander, PhD, Jennifer Craig-Muller, Alireza Atri, MD, Thomas Beach, MD, PhD, Richard Caselli, MD, Yi Su, PhD, Eric Reiman, MD. University of Arizona; Banner Alzheimer's Institute; Banner Sun Health Research Institute; Mayo Clinic; Arizona State University; Arizona Alzheimer's Consortium.

Specific Aims:

We will address the following specific aims: 1) to make available for research blood-based biomarker assay results from clinically well-characterized, older adult participants enrolled in the ADCC/ADRC Clinical Core; and 2) to help develop and implement novel methods for evaluating the association of blood-based biomarkers with cognitive and neuroimaging scans to better evaluate age-related, cognitive decline and preclinical AD risk. Additionally, this study provides added value by providing an opportunity to help: 1) create a unique dataset to support cognitive aging and AD research across Arizona, 2) explore how blood-based biomarker measures relate to demographic and cognitive differences in older adults; 3) evaluate how biomarkers ultimately relate to post-mortem brain pathology, and 4) support new external grant proposals on aging and AD risk.

Project Description:

This proposal requests support for a cross-institutional, collaborative research effort, including investigators from the University of Arizona, Banner Sun Health Research Institute, and Banner Alzheimer's Institute. The proposal will support Arizona Alzheimer's Consortium research to advance our ability to clarify and compare the cognitive and biological changes associated with aging in the presence or absence of Alzheimer's disease (AD). Participants for this proposal will include clinically well-characterized older adults that are either active in our existing ADCC or are newly enrolled into our ADRC Clinical Core, which includes those from developing Native American and Hispanic/Latino cohorts, as well as those enrolled in our Brain and Body Donation Program (BBDP). We propose to utilize standardized assay procedures developed by our center collaborators to obtain state-of-the-art blood-based biomarkers of amyloid and tau for comparison to concurrently collected tests of cognitive function and magnetic resonance imaging (MRI) scans of brain structure, function, and connectivity from the ADCC/ADRC Biomarker and Clinical Cores. It is expected that the resulting data from the blood-based biomarker assays proposed in this research effort will complement our ADCC/ADRC data, will augment and expand current efforts to evaluate the early preclinical effects of AD and will assess how these effects differ among diverse older adult groups, with important implications for identifying effective AD prevention therapies.

Background and Significance:

The population of older adults is expected to grow rapidly over the next two decades and with this growth of the aging population, it will be increasingly important to respond to the associated increases in AD, both in Arizona and nationally. Recent advances in blood-based biomarkers have allowed the pathological features of amyloid- β (A β) plaques and tau neurofibrillary tangles to be detected in living humans from collection of a blood sample. We have developed extensive experience in the Arizona ADCC with the application of blood-based biomarkers for amyloid and tau, providing valuable and less invasive markers of AD pathology in individuals prior to the development of cognitive symptoms. This proposal leverages the expertise and infrastructure of the Arizona AAC, ADCC BIFB Core, and our newly proposed ADRC Biomarker Core, allowing us to efficiently combine fluid and brain imaging biomarkers of amyloid and tau with other biomarkers and cognitive measures. Blood-based biomarkers will be integrated into our ongoing

ADCC/ADRC efforts with both cognitively normal and impaired participants who are followed annually in our Clinical Core. This work will serve to further establish and expand the valuable research findings derived from our ADCC/ADRC efforts, while providing critical data needed to inform analyses and statistical power for the use of biomarkers in prevention trials. Together, these data will also provide a valuable resource for developing and testing new biomarkers in relation to blood-based and neuroimaging measures and ultimately to neuropathology findings.

Preliminary Data:

Using ongoing supplemental funds from the NIA, our Arizona ADCC BIFB Core (AG019610-19S1; Core Leader: Alexander; ADCC PI: Reiman) has begun to implement plans for standardized acquisition of PET and MRI scans, together with fluid biomarkers from cerebrospinal fluid and blood in our ancillary cohorts that are National Alzheimer's Coordinating Center (NACC) compliant. With submission of our center grant renewal to establish an ADRC, which includes a new Biomarker Core, we plan to obtain blood samples, as well clinical/cognitive assessments and MRI scans on all center participants enrolled in our Clinical Core. Efforts to obtain amyloid and tau PET and MRI scans in 172 cognitively unimpaired BBDP participants, as well as 72 ADCC Clinical Core participants, including patients with mild AD, mild cognitive impairment and healthy controls, is currently underway.

Experimental Designs and Methods:

This project proposes to leverage existing data, samples and resources from our ADCC/ADRC study, including our Native American and Hispanic/Latino cohorts. All ADCC/ADRC participants receive annual clinical and cognitive assessments, and many have agreed to post-mortem donation of their brain to support aging and AD research, as part of the Arizona ADCC/ADRC. The pending ADRC Biomarker Core includes several collaborators from this AAC proposal (Alexander, Atri, Beach, Reiman, Su). As part of this core, we expect to collect MRI scans and blood samples in virtually all participants enrolled in our Clinical Core, including from the Native American and Hispanic/Latino Cohorts. This separate AAC-funded project will provide complementary support to obtain blood-based biomarker measurements of amyloid and tau, making these AD biomarker results available for nearly all Clinical Core participants. Data collected from the proposed biomarker assays will be uploaded to the ADCC/ADRC Database for archiving and will be linked to each participant's annual clinical and cognitive scores, as well as their baseline MRI scan data.

Proposed One-Year and Long-Term Outcomes:

The data acquired by this project, when combined with our ADCC/ADRC database, will further support projects investigating blood-based biomarkers in the context of AD risk and how these effects are influenced by differences in demographic diversity. These studies reflect collaborations focused on developing externally funded grant proposals, as part of a multi-disciplinary, collaborative research programs that will leverage the expertise of investigators across the Arizona ADCC/ADRC. The proposed research will provide a novel and rich dataset leading to published findings to advance our understanding of how blood-based biomarkers are associated with the risk for dementia and cognitive decline. Importantly, it is expected that this dataset will provide essential pilot data to support new proposals by Arizona researchers for external NIH funding. Specifically, this project will provide key data to help support new grant applications that utilize amyloid and tau plasma biomarkers of preclinical AD.

Year End Progress Summary:

We made significant progress in achieving the aims and goals of this project. During this reporting period, we focused on selecting the appropriate blood-based biomarker assays, determining what samples to assay, and putting the necessary institutional arrangements in place to obtain the

assay results. We also continued our parallel work of acquiring PET and MRI scans on participants so that we have the key data for comparison with the blood-based biomarker data.

We utilized standardized protocols and procedures compliant with national initiatives known as SCAN for MRI and PET imaging using both amyloid and tau tracers. We continue to have access for use of florbetapir, PIB, NAV-4694, and florbetaben for amyloid PET imaging and flortaucipir and MK-6240 for tau PET imaging, as part of the Biomarker Core. We continue to work closely with Dr. Tatiana Faroud's team at NCRAD to send our blood and CSF samples from participants for processing and storage. To support this ongoing collaborative work, material transfer agreements with NCRAD have been in place for all acquisition sites, including BAI, BHSRI, and UA. This work provided the complementary imaging data and blood samples needed to complete the work supported within this proposal.

We engaged with Dr. Jeffrey Dage from Indiana University (IU), a leading expert in blood-based biomarkers, to discuss the assays available including their sensitivity, specificity, and availability. In early 2021, Dr. Dage was in the process of scaling up a lab at IU, as part of a national effort working with NCRAD, to provide biomarker assays for Alzheimer's Disease researchers to have a reliable and consistent access. Working with Dr. Dage, we determined that Amyloid Beta 40 (A β -40), Amyloid Beta 42 (A β -42), neurofilament light (NfL), and ptau-181 would provide valuable data to help understand how these well-established BBBMs relate to clinical disease progression.

Given that we were able to obtain all 4 biomarker assays on 318 samples, we carefully selected samples based on neuroimaging available, brain donation status, age, demographics, and cognitive status with the overall objective of matching non-Hispanic controls with all other groups. After selecting the samples, IU informed us that they encountered supply chain issues related to the Covid-19 pandemic for A β -40 and A β -42 assays and would not be able to complete the assays within the original project timeline. Given this unexpected challenge, we modified the arrangement with IU to complete NfL and ptau-181 assays on more samples (484 samples). With the expansion in number of samples, we leveraged the unique opportunity to assay multiple timepoints from the same participants to track the changes overtime. The table above shows the ethnicity breakdown of the participants that were selected for the final biomarker assays, which included participants enriched from Native American and African American communities. Of the total 350 participants, 68% were healthy cognitively unimpaired adults and all participants are being followed with clinical and cognitive assessments annually.

Ethnicity	Count
American Indian or Alaska Native	48
Asian	11
Black or African American	29
Other	3
Unknown	9
White	250
Total	350

With the assays provided by IU for the NfL and ptau-181 data for this project, we plan to conduct analyses of the results to evaluate biomarker differences in relation to race/ethnicities, cognitive status, and correlation with neuroimaging data, as well as disease progression over time. In addition, we plan to explore obtaining the A β -40 and A β -42 assays for these samples in our future work to relate the current findings for NfL and ptau-181 to the amyloid biomarkers, as well as additional blood-based biomarkers, as they become available. It is expected that the biomarker results obtained from this project will provide an outstanding opportunity to better understand how blood-based biomarkers can be utilized to help detect and track the earliest effects of Alzheimer's disease, with the potential to support new intervention and prevention studies.

**BANNER SUN HEALTH RESEARCH INSTITUTE
PROJECT PROGRESS REPORTS**

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 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), and colleagues from each of the participating Alzheimer's Consortium sites. Banner Sun Health Research Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

1. To provide the foundation of a shared resource of separated cells to researchers within and outside Arizona.
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.

Preliminary Data:

Co-PI Thomas Beach is Director of the Banner Sun Health Research Institute's Brain and Body Donation Program (BBDP), a clinicopathological study of aging and neurodegenerative disease based in Sun City, AZ since 1987. The BBDP has made rapid autopsy a priority, with a 3.0-hour median postmortem interval for the entire collection, which allow rapid acquisition of high quality brain samples. The PI, Geidy Serrano, has been operationally leading this project since 2015 and is responsible for the successful development of methodology to date.

To date, 443 autopsies have been performed by the Brain and Body Donation Program (BBDP) since the funding start date for this continuing project (July 1, 2016). Of these, tissue from 146 subjects has been used to generate WSDS. The BBDP continued their operations during the COVID pandemic and in the current funding year (beginning July 1, 2021) performed 68 autopsies. However, due to the high percentage of COVID positive cases in the community, and therefore our participants, we only performed cell suspensions from 16 of those autopsies. All

autopsies were screened for SARS- CoV-2 and none of the 16 suspensions were positive for SARS- CoV-2

Experimental Designs and Methods:

Single cell suspensions are generated from frontal cortex obtained at autopsy. Approximately fifty grams of grey matter are dissected out from fresh frontal lobe slices bilaterally. The samples are then immediately processed to produce single-cell suspensions. The method uses enzymatic digestion with Accutase for 4 hours at 4°C of fresh tissue minced with a razor blade, followed by mechanical disruption by repetitive pipetting. Myelin, neuropil and other cellular debris is removed by Percoll density gradient centrifugation. Final suspensions are then aliquoted for cell banking in cryopreservative solution and stored at -80°C for later experimental usage and quality control (QC) assessments (method manuscript in preparation).

Phenotypic characterization by H & E staining and Immunohistochemical staining confirms the presence of these cell types with antibodies specific for neurons (NeuN), astrocytes (GFAP) and microglia (Iba1). Once cell types are identified using the most suitable antibodies, cells are sorted with fluorescence-activated cell sorting (FACS) or magnetic beads. RNA from sorted cells is extracted, and 100 ng from each sample is used for qPCR. β actin is used as a housekeeping gene, and probes for MAP2, GFAP and IBA1 are used to confirm the presence of cells of interest and to estimate their enrichment compared to the remaining cell population. Manual bar coding using SplitBio technology allow single cell sorting. Further analysis of cell suspensions using next generation RNA sequencing (RNA-Seq) is used to analyze sorted cell-specific population or single cells.

Specific Aim 1: To provide the foundation of a shared resource of separated cells to researchers within and outside Arizona.

Over the last couple of years, we have collected enough evidence to show WSDS generated at the Banner BBDP are suitable for multiple experiments that could lead to better understanding of single cell or population changes in aging and neurodegenerative disorders associated with aging. We are now actively promoting this resource on our website and in meetings. A methodology paper was already published in Med Archives and a modified version was accepted in Journal of Tissue Science and Engineering, Volume 12: 4, 2021.

In addition, more high-profile projects were undertaken to further establish the importance of the general approach and to increase awareness of the resource among the neurodegenerative disease scientific community. The resource is providing single cells suspension for studies independently funded by the MJFF and PSP foundations aiming to studies transcriptome sequencing from enriched human cell-specific populations and single cells. A summary of our results will be posted in each foundation websites and therefore contribute the resource promotion. For these projects most of the identified genes that are differentially regulated early in disease are related to translation, transcription, and DNA/RNA repair. Another important group of genes that seems to be downregulated are genes associated to cysteine and glutathione redox balance in astrocytes, ion binding proteins, creatine kinase activity and transmembrane signal receptor.

Specific 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).

During this funding year we have done multiple FACS and magnetic beads experiments with different antibodies aiming to improve cell enrichment. We have used different cell specific markers to allow us to sort different cell populations (astrocytes and neurons). We have sorted a total of 50 cases and the RNA from the enriched populations was isolated and sent for RNA sequencing (RNA-Seq). The analysis results are pending, but preliminary data suggest that we should be able to correlate brain pathology with multiple disease-regulated transcripts such as aquaporins and glutamate transporter in astrocytes.

Another methodological approach that we are continuing to work on is using WSDS for single cell RNA-Seq that could potentially be the method that will give the greatest advances in the understanding of cell-type-specific gene expression changes. Unfortunately, the most common approach, using a 10X Genomics droplet-based platform, seems not be appropriate for human WSDS because the cells appeared to be damaged by the process. We hypothesized that cell size and the neurite presence in the suspension is our major challenge with this approach. We are now trying new approaches that will be gentler approaches for single cell sequencing, such as manual bar coding using SplitBio technology. We also compared our single whole cell to single nuclei RNAseq to see how it will complement our sorting experiments. This year we were able to create successful sequence libraries on over 50,000 cells from a total of 30 donors. Complete analysis results are pending.

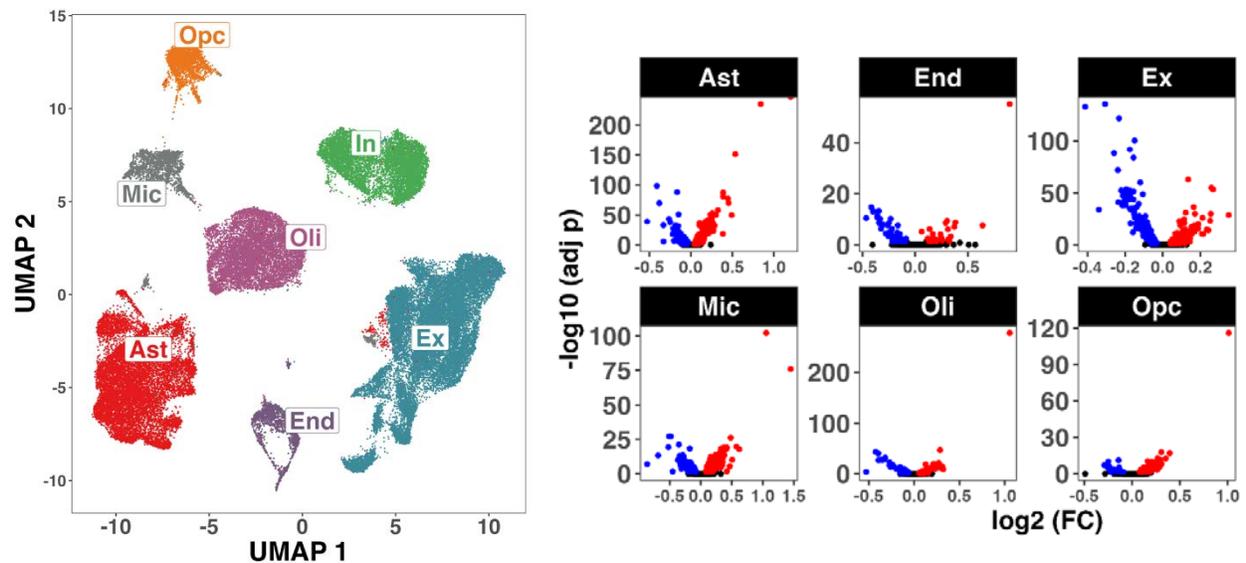


Figure 1. *t*-SNE plots of single nuclei from and Volcano plot to represent regulation per cell type showing differentially expressed genes after adjustment. Each point is a cell and is colored by its cluster assignment by cell types (left). When cell types were compared in AD vs PSP multiple genes were Down-regulated genes are blue and up-regulated gene in red (right).

Year End Progress Summary:

1. Over the last couple of years, we had collected enough evidence that show WSDS generated at the Banner BBDP are suitable for multiple experiments that could lead to better understanding of single cell or population changes in aging and neurodegenerative disorders associated with aging. We are now actively promoting this resource in our website and meetings.
2. Further analysis of cell suspensions using next generation RNA sequencing (RNA-Seq) will be done using gentler approaches such as manual bar coding and magnetic beads covered with a surface epoxy group for manual cell separation. Both approaches seem very promising and we are already in the process of testing the protocols.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Establishing a network for prodromal synucleinopathy research in Arizona. David Shprecher, DO, MSci; Joyce Lee-Iannotti, MD; Parichita Choudhury, MD; Pooja Rangan, PhD. Banner Sun Health Research Institute; Banner University Medical Center-Phoenix; Banner Alzheimer's Institute.

Background and Significance:

Approximately 2 million older Americans suffer from Parkinson's disease (PD), dementia with Lewy bodies (DLB), or multiple system atrophy (MSA), collectively referred to as the "synucleinopathies." The estimated health care cost is \$14B per annum. (1) Idiopathic rapid eye movement REM sleep behavior disorder (iRBD), a parasomnia characterized by a lack of motor inhibition during REM sleep in absence of a secondary cause, (2) is strongly associated with later development of synucleinopathies. (3) Phenoconversion risk is approximately 20-50% within 5 years of RBD symptom onset, rises to 50-75% in 5-10 years, and 80-92% in long-term follow-up. (4,5-10) Several biomarkers have been identified as sensitive but not specific for Parkinson's disease in iRBD including quantitative changes in olfaction (5), abnormal quantitative motor testing, and abnormal DAT SPECT scans. (6,7) Identifying patients with idiopathic RBD at highest risk for phenoconversion to neurodegenerative diseases would be pivotal for neuroprotective strategies. As prevalence of iRBD is less than 1% (11), collaboration with sleep medicine clinicians is crucial for recruitment.

Specific Aim 1: To establish a network among Phoenix area sleep medicine providers for referral of iRBD patients into research registries. We will implement a plan to network with various sleep centers across the valley to incentivize RBD patients' participation in research registries and trials at the local, national, and international levels. Phoenix is a large metropolitan area, consisting of approximately 2 large, academic sleep centers and 18 smaller, non-academic centers. We will target these smaller, non-academic sleep centers in the community to increase RBD subject recruitment.

Specific Aim 2: To validate the REM sleep behavior disorder severity scale. This will be done using data from nearly 250 participants with RBD who have had longitudinal assessments through the NAPS Consortium.

Preliminary Data:

Dr. Shprecher has previously conducted broad-based observational research in the field of neurodegenerative disease (11-17) including two recent studies on the prevalence of iRBD. Dr. Lee-Iannotti is a neurologist boarded in sleep medicine and directs the sleep medicine program at Banner University Medical Center-Phoenix. Dr Choudhury is a neurologist with subspecialty training in behavioral neurology and recent publications in the field of neurodegenerative disease (18-19). All three serve as site investigators for the NAPS consortium study at BSHRI. Thus far, 12 participants have been consented at BSHRI and over 250 participants have been enrolled across the entire NAPS consortium.

Experimental Designs and Methods:

Specific Aim 1: Education and networking will be initiated with the non-academic sleep centers throughout the Phoenix valley to ensure that polysomnogram reports include information needed to diagnose iRBD, and to encourage referral of iRBD patients to participate in clinical research.

During the first 6 months of the funding period, our staff completed in person and telephone outreach to our area nonacademic sleep medicine programs. Key learnings from this time period were that staff-to-staff outreach is not effective. Focus was then shifted to two primary mechanisms. First, direct communication from PI/co-investigators to fellow clinicians to engender interest in one-on-one meetings and potential study referrals. During the second half of the funding period, a total of two group lecture-based conversations about pitfalls of RBD diagnosis, and importance of research referrals, were held with outside sleep medicine clinicians at the BUMC-P Sleep Center. The second mechanism was direct search of electronic medical record for RBD diagnosis (excluding those with neurodegenerative disease or dementia diagnoses) to identify patients already followed at the BUMC-P sleep center, then involve sleep center staff in contacting them on behalf of Dr Lee-Iannotti to encourage them to schedule a conversation with the study coordinators about research opportunities. Several hundred individuals were identified through this mechanism, and it is now clear that additional funding will be needed to complete the work of contacting all of them.

During the second half of the funding period, a total of two group lecture-based conversations about pitfalls of RBD diagnosis, and importance of research referrals, were held with outside sleep medicine clinicians at the BUMC-P Sleep Center.

Specific Aim 2: Development of validated tools for measuring and tracking the severity of RBD is essential for measuring outcome in clinical trials of symptomatic therapy and to prevent sleep related injury. Data collected as part of the NAPS consortium assessments (~250 participants) will be utilized to compare clinician global impression of severity (CGI-C) with non-polysomnogram based scales. Specifically, we will determine the following relationships:

- 1) Internal consistency and construct validity of the RBD severity scale questions (RBDSS)
- 2) Correlations between patient and bed-partner estimate of severity on the RBD severity scale
- 3) Concurrent validity of the Mayo sleep questionnaire with CGI-C and RBDSS

The study has been completed and presented in abstract form at several meetings including the American Academy of Neurology, American Academy of Sleep Medicine, and the International Lewy body dementia conference (also accepted to be presented August 2022 at the Alzheimer's Association International Conference and Sept 2022 at the International Congress of Parkinson's Disease and Movement Disorders.) The manuscript is in preparation for peer-reviewed publication.

Proposed One-Year and Long-Term Outcomes:

By April 2022, we expect to have completed statistical analysis and submission of data for at least two abstract presentations and one peer-reviewed manuscript publication.

By the end of year one, we expect to engender RBD research referrals (aim 1) from at least 8 sleep medicine programs across Arizona.

By July 2023, we expect to

1. Document continued, regular research referrals from the majority of sleep medicine programs identified in the first year.
2. Begin additional data mining projects from the NAPS Consortium.
3. Consider prevention trials in these cohorts.

Year End Progress Summary:

Efforts of the investigators are now shifting to focus on recruitment and site level activities for the Michael J Fox Foundation Parkinson's Progression Markers Initiation (PPMI). This is a very large international observational study with comprehensive clinical and biomarker assessments of

early-stage Parkinson disease including a prodromal cohort with iRBD. Each site is expected to recruit 20 iRBD participants per year. PPMI is now accepting proposals to fund time and effort of clinicians and staff to support recruitment of iRBD patients from partner sleep medicine programs. We will now arrange funding of at least 5% FTE for Dr JLI to continue in her current role initiated from the AAC grant and continue to support our outreach to sleep medicine clinicians in the community, identification of iRBD patients for research from our sleep clinics, and to support review of sleep studies to confirm iRBD diagnosis (review for this purpose is very time intensive and is not always fully supported by clinical revenues). This additional funding thru PPMI will also allow us to support staffing to contact the individual patients identified from periodic clinic record searches at both of our sleep clinic locations in Sun City West and downtown Phoenix. The PPMI study is also developing a framework to fast track iRBD participants for recruitment into Parkinson disease prevention trials as promising new study drugs are identified.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Patient-based postmortem fibroblast banking for translational research. Geidy Serrano, PhD, Thomas G. Beach, MD, PhD, Rita Sattler, PhD, Suet Theng Beh, PhD. Banner Sun Health Research Institute (BSHRI); Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Specific Aims:

Aim 1: To build on what we have already established in last two years to bank and characterize more scalp tissue-derived fibroblasts from donors with neurodegenerative diseases or without neurodegenerative diseases. The goal is to increase the number of cryogenic cells in each apolipoprotein genotype from Alzheimer disease (AD) or non-AD cases.

Aim 2: To bank human iPSC lines generated from four of our banked cases: one from an ALS c9 mutation case, one from an ApoE4/4 AD case, and the other two will be from ApoE 3/3 cases (one with an AD neuropathological diagnosis and the other from a normal control case).

Aim 3: To develop a protocol to directly reprogram human fibroblasts to neurons.

Background and Significance:

AD is a major neurodegenerative disease in the aging population. Although tremendous progress in understanding and diagnosis of the disease has been made in the last three decades, there is still no effective disease-modifying treatments. Many researchers have agreed that improved experimental models are needed to better recapitulate the sporadic AD disease pathways in human brains, as animal models carrying mutated genes identified in familial AD may not be adequate for sporadic AD. To create better research models for AD, human neural cell or organoid cultures generated from stem cell technologies have been increasingly used (1-3). These models can be made from procedures that generate somatic cells from inducible pluripotent stem cells (iPSCs) or procedures directly transforming somatic cells to other somatic cells.

Skin fibroblasts are the most frequently used somatic cell types for the stem-cell based procedures. At BSHRI, the Brain and Body Donation Program (BBDP) banks postmortem tissues from 50-60 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 the longitudinal aging study while they were alive and received clinical and neuropsychological assessment yearly.

Preliminary Data:

We have developed the procedures to yield consistent explant and fibroblast cultures in the first year of the Human Cells Banking Program. Since then, we have been successfully banking scalp-derived fibroblasts from 30 autopsy cases and a manuscript has been published in *Cells* (Beh et al., 2020). To date, the mean and standard deviation of the days from autopsy to cell cryoprotection were 57.3 ± 24.3 days. The culture was started from dermal explants. The average number of days for skin cells to grow out were 12.7 ± 7.0 days. Cultures were maintained in FibroLife media with supplements twice a week. Expansion of proliferating fibroblasts were passaged three times. At confluency of passage 3 cultures, cells were collected, counted, and aliquoted for cryoprotection and pelleting. The protein and gene expressions of the cell pellets were characterized by immunofluorescence, western blot, and qPCR.

During this funding period, to avoid culturing of fibroblasts from the autopsy tissues that carried SARS-CoV2, we needed to modify our regular procedure. This delayed the processing of postmortem scalp tissues until the SARS-CoV2 PCR test confirmed the absence of the virus. Therefore, since July of 2021, the number of autopsy cases used for isolation of the fibroblasts was reduced as well as the success rate due to the prolonged wait time for the test results. In a

total of 30 months since the establishment of the HCCTR, we have banked 1121 cryogenic vials of well characterized scalp-derived fibroblasts.

Experimental Designs and Methods:

In this proposal, we will follow our established protocol to obtain explant and fibroblast cultures and bank passage 3 fibroblasts from an additional 35-40 cases. We will also bank cryoprotected scalp tissues. The tissue banking will be assessed for storage duration that viable cells could be produced. We will keep 1/3 of the tissues from each case in cryoprotectant and stored at -20°C. The assessment will be carried out at 30, 60, and 90 days of cryopreservation. At the designated time, cryoprotected tissues will be thawed and processed for explant culture according to our procedure. We will use two cases for each time points in a total of 6 cases. Culture will be assessed for the rate of cell proliferation. We will also assess cases from longer term storage if they become available.

Proposed One-Year and Long-Term Outcomes:

During the proposed funding period, we will aim to bank fibroblasts and scalp tissues from a total of 35-40 autopsy cases. This is 3-4 cases each month for 10 months as each case takes approximately 2 months to maintain. Cases will be selected for culturing based in part on antemortem genotyping for APOE and other genes of interest. We will use the last two months to complete characterization. As the cases selected for iPSC generation have already been banked, we will be able to start immediately. We anticipate that they will be completed 6-8 months into the project. Our long-term goal is to be able to build a large patient-based fibroblast and iPSC banking program for both familial and sporadic neurodegenerative disease research.

Year End Progress Summary:

1. Since being established in September of 2018, we have successfully banked fibroblasts from 77 scalp tissues out of 126 donor cases that we processed. A total of 1581 million fibroblasts were collected and banked (cryopreserved) from 77 donors.
2. During this funding period, we successfully banked fibroblasts from 25 scalp tissues out of 52 donor cases that we processed. 6 cases were excluded during culture after donors tested positive for SARS-CoV-2. A total of 315 million fibroblasts were collected and banked (cryopreserved) from 25 donors.
3. The aliquots of cryoprotected P3 fibroblasts stored in liquid nitrogen were tested for the yield of viable cells after defrosting. The revival rates defined by the percentage of live cell counts in total cell numbers were > 95%, and cells attached and proliferated within 24 hours.
4. As part of quality control, our banked fibroblasts were characterized by the expression of a panel of fibroblast markers by qPCR. These genes included fibroblast activation protein (FAP), fibronectin (FN1), Thy-1 cell surface antigen (THY1), and Vimentin (VIM). The results of mRNA analysis showed positive expression of FAP, FN1, THY1, and VIM. We also assessed the frequency of keratinocytes present in our P3 fibroblast cultures. To further validate the identity of the banked cells, we characterized cells at passage 3 by a panel of antibodies to detect, by immunofluorescence, the fibroblast expressing proteins, including fibroblast surface protein (FSP), fibroblast activation protein (FAP), fibronectin, alpha-smooth muscle actin (α -SMA), and vimentin. Positive control of fibroblasts and negative control of keratinocytes from a commercial source was included in the study. An antibody for cytokeratin was used as the marker of the keratinocytes. Based on immunofluorescence intensity and morphological features we confirmed that all our banked cells were consistent with the features of the fibroblasts.
5. The success rate has been reduced during this funding period due to:

- (a) changes to process the autopsied scalp cells after receiving diagnostic SARS-CoV-2 results. The average tissue processing interval (TPI, hours of delay from death to scalp processing) from 52 donors was 232 hours compared to 13.5 hours before the COVID-19 pandemic. We found that the success rate was affected by the delay of tissue processing. We detected a positive correlation between FN1 Δ Ct and TPI ($\rho = 0.444$, $P = 0.0180$), indicating that the longer the cells took to grow out of explants, the larger the FN1 Δ Ct values, indicating lower FN1 expression in the P3 cells. Similar results were found in VIM Δ Ct with TPI ($\rho = 0.430$, $P = 0.0222$).
 - (b) A low success rate from newly trained technicians. We found that the adherence of the explants in the culture contributes to a successful culture, so we have developed a new protocol to improve the technician's success rate.
6. During this funding period, our cell core has provided to four groups of research scientists with fibroblasts from specific APOE genotype, gender, and disease category, from which three of them were reprogramming fibroblasts into stem cells. A total of 21 million fibroblasts from 24 cases were sent out to support four studies. Scientists in the biomedical field have also been inquiring about our banked fibroblasts.
 7. Another methodological approach that we are continuing to work on is using RNA-Seq which could potentially be the method that will give the greatest advances in the understanding of specific gene expression changes from donors. Complete analysis results are pending.
 8. During this year, two more projects were undertaken to further establish a potentially better patient-based cell resource for disease modeling and drug discovery in neurodegenerative disease. We used a combination of small molecules to direct reprogramming of fibroblasts into neurons and a multipotent somatic stem cell, human skin-derived precursor cells (hSKPs). A challenge for *in vivo* direct reprogramming is to know that the low efficiency of conversion and the poor survival of directly reprogrammed cells after transplantation. Our studies aim to develop and provide a rapid and efficient transgene-free approach from human fibroblasts which has great potential for drug screening and transplantation treatment of neurodegenerative diseases. These direct reprogramming methods will be continuously developed to generate a large scale of patient-based induced neurons or hSKPs for clinical and research uses. Further analysis of the regulatory genes and signaling pathways in direct reprogramming will be done using RNA-Seq. In addition, efficient cell sorting technology will be developed to purify the directly converted cells.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Enhancing Clinical and Biological Characterization of The Longevity Cohort Study: Global Staging and Biospecimen Banking. Alireza Atri, MD, PhD, Angela Kuramoto, RT, MHA, Kathy O'Connor, MS, Christi Belden, PsyD, David W Coon, PhD, Briana Auman, PsyD, Autumn Arch, Geidy Serrano, PhD, Thomas Beach, MD, PhD, Kewei Chen, PhD, Michael Malek-Ahmadi, PhD. Banner Sun Health Research Institute; Arizona State University; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Specific Aims:

- 1) Clinical research phenotyping (adapted to continued COVID-19 measures and restrictions, see AIM 1 design/methods below), 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), and to adapt LCS procedures and measures to remote formats.
- 2) Blood collection and biospecimen banking of 30 cc of plasma from study participants to be made available for collaborative research opportunities and for preliminary data investigations for grant applications; and referral and co-enrollment of participants in other cognitive aging and biomarker studies.
- 3) 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 15th year, "The Longevity Study: Learning from Our Elders Cohort" (LCS) is a unique Phoenix metropolitan area-based longitudinal study of psychosocial dynamics, lifestyle, physical activity, and cognitive function in successful aging of independent, community-dwelling, older individuals. In the 2021-2022 funding year, the LCS adapted and modified its operations due to pandemic, and was able to continue this unique longitudinal biopsychosocial study of longevity and successful aging, in the oldest-old (aged 85+). Since its inception, the LCS has enrolled 1552 subjects, and currently follows 544 active participants. The average age of participants is >80; and 56% of active subjects 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.

Participants undergo annual interviews and assessments, performed either at the BSHRI Center for Healthy Aging or in the participants' residences (through televideo). The study captures a wealth of sociodemographic, medical, cognitive, physical, personality, lifestyle, and psychosocial data; and contains a strong portfolio of psychosocial variables with wide breadth and depth that are yielding publications. However, until recent years through matching grant support by AZ DHS AAC grant funding, the LCS's potential for impact and future funding had been limited by a lack of clinical research characterization of the global status of participants (e.g. via a process such as the Clinical Dementia Rating, CDR, assessment), and by the availability of biospecimens to conduct collaborative and cutting-edge research to link bio- and psychosocial factors in the study of successful aging in the older, and the oldest old.

Project Description:

This proposal aims to continue on the path of obtaining important longitudinal clinical phenotyping (staging) and bio- characterization data, co-enroll and refer LCS participants to observational, biomarker and other studies; and to perform exploratory analyses, that will

substantially enhance potential for biopsychosocial collaborative research, particularly related to cognitive resilience and reserve, and funding prospects and impact. Availability of these additional data and biospecimens, and co-enrollment and referral of participants to impactful cognitive aging and biomarker studies (e.g. see below regarding 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 will provide 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, will improve recruitment and dual/co-enrollment of cognitively unimpaired subjects into other impactful studies such as the Brain and Body Donation Program (BBDP). For example, increasing efficiency and quantity of dual enrollment between LCS and BBDP serves to support continued enrollment of cognitively normal elderly, 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, bio, clinical, psychosocial, and, ultimately, pathological data.

Experimental Designs and Methods:

Aim 1: Clinical Phenotyping (adapted to COVID-19 measures and restrictions using televideo and hybrid visits). Newly enrolled participants will continue to be required to have a study informant; both will undergo CDR by a certified rater (~1-1.5 hours). In consideration of the COVID-19 measures and restrictions (C19PDM) in place, and precautions and sequelae to be expected through 2022-2023, we will continue to employ televideo or hybrid formats as needed. To account for attrition, we will enroll ~50-60 new participants in the coming year. Additionally, active participants deemed to be at higher risk of cognitive impairment will continued to be identified the algorithm, that includes risk factors, self or informant report, MoCA score of <26 at baseline, or a ≥ 2 point drop in MoCA from any previous score, to undergo CDR assessment (N~180-200). We will incorporate CDRs for 102 active participants dual-enrolled in LCS and BBDP. All participants will be assigned a global stage (e.g. cognitively unimpaired, subjective cognitive decline, MCI, mild dementia) based algorithm criteria or the CDR (N=392). So far 446 CDRs have been performed (not including those of BBDP co-enrolled participants, N=102).

Aim 2: Banking of plasma (N~250 in FY23 adapted to C19DPM restrictions and sequelae) expect ~60% of participants to be able to donate 30 cc for plasma aliquoting (per BBDP processing);

Aim 3: Utilize ML to identify and validate measures, and patterns of biopsychosocial and clinical characteristics associated with better cognition, function, behavior & satisfaction in the oldest old.

Proposed One-Year and Long-Term Outcomes:

Our goals are to continue LCS assessments and clinical phenotyping, blood collection, collaboration with affiliated studies and referrals, and to begin preliminary analysis, using ML methods, of data. Progress in FY 2021-22, despite Covid-19 disruptions to operations (mostly impacting blood specimen collection and enrollment of new participants) is summarized below. We expected to added to continue progress by further longitudinal_clinical phenotyping of participants; by continuing, as needed, the adapted C19DPM study procedures and measures we have developed during the pandemic; and by collection, characterization and biobanking of additional plasma samples. We will continue to refer and co-enroll LCS participants in impactful cognitive aging and biomarker studies, and also 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.

Year End Progress Summary:

During the funding period there has been great progress made to fulfill the specific aims of the grant. We adopted televideo assessments along with in-person visits, and 632 study visits were completed during the funding period. The LCS has 544 active participants (enrolled 1,552 since inception). Prior to COVID-19 physical distancing measures, approximately 45-60 visits were conducted per month, and new participants were enrolled to offset attrition, which is 4.4% per year (annualized over the 14-years; mostly due to death and moving from AZ). During 2021-22 our monthly visits ranged from 32-77. Approximately 67% of participants are female, 328 are ≥ 80 years of age, 218 are ≥ 85 , 100 are between 90-99, and 2 are 100 years or older.

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 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. Additionally, in the 2021-2022 funding year, there were a total of 190 referrals from the LCS to other ongoing research studies, including 63 to the BBBDP and 2 to the newly established and NIA-funded ADRC cohort study.

Progress made on Specific Aim 1 –

During the 2021-2022 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 (e.g. MoCA, scores ≥ 27 regardless of age and no decline in score of two or greater points compared to a previous score) were also required to have a study partner to undergo the CDR interview. Over 460 CDR have been performed in the LCS (excluding those of BBBDP co-enrolled participants, N=102); 161 CDRs were performed in 2021-22; and 158 CDRs were longitudinal CDRs. As expected, the vast majority of active LCS participants (>96%) are, thus far, 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 >56% 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) continues to be 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. Since inception, we have collected 403 samples (goal 350-400) with 69 new samples collected this year.

Progress made on Specific Aim 3 –

Dr. Atri collaborated with Dr. Chen to preliminarily explore a variety of ML analyses utilizing BBBDP longitudinal cohort data. Application and validation of ML methods is an ongoing aim.

In summary, there has been excellent progress made on the grants aims. With continued progress on these aims in 2022-23 we will be well-positioned to have foundational and necessary data for additional publications and to support further grant applications in 2023.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Mild Behavioral Impairment, MBI: Clinicopathological Characterization, Correlations and Course. Danielle Goldfarb, MD, Kewei Chen, PhD, Thomas Beach MD, PhD, Michael Malek-Ahmadi, PhD, Alireza Atri, MD, PhD. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium

Specific Aims:

1. To characterize and correlate associations between topographical distribution and burden of neuropathological changes (AD/ADRD) and nature (presence and profiles) and progression of neuropsychiatric symptoms (NPS) (defined using the Neuropsychiatric Inventory Questionnaire (NPI-Q) and Geriatric Depression Scale (GDS)) in mild behavioral impairment (MBI).
2. a) Delineate the MBI trajectories (total score on NPI-Q, and salient measures and covariates including the GDS and Hamilton Depression Rating Scale, HAM-D) using mixed models for repeated measures (MMRM) multivariate methods.

b) Define algorithms whether patterns and combinations of clinical features, demographic characteristics, and neuropathological changes (type, location, severity) are associated with particular MBI profiles or trajectories.

c) Utilize learnings from results of Aims 1 and 2a/b to develop and assess the fit of latent class models that would be consistent with causal relationships between clinical characteristics and neuropathological changes to influence development, nature, and progression of NPS in MBI.

Background and Significance:

There is increasing recognition that new-onset NPS in older adults often begin during the 'preclinical' period prior to cognitive decline and may be the index manifestation of AD/ADRD. While a growing body of research focuses on elucidating the neurobiologic substrates and clinical correlates of MBI during life, there have been no published studies characterizing the neuropathological correlates of MBI via autopsy data, and this understanding will provide insights into the neurobiological basis of MBI, identify a subset of patients vulnerable to MBI who may benefit from early detection and interventions.

Project Description:

The goal of this project is to characterize the clinicopathologic characteristics, correlates and clinical course associated with MBI utilizing analysis of prospectively collectively data from the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND). We will characterize the neuropathologic correlates of MBI by exploring the associations between the presence, location, and severity of neuropathologic changes in multiple brain regions, and hypothesize that non-demented (cognitively unimpaired and mild cognitive impairment) participants with MBI symptomatology will have a substantially greater burden of neurodegenerative brain changes in key regions compared to those without MBI. We will then utilize mathematical techniques (including ML) to explore relationships between neuropathological changes (type, location, severity) and emergence and progression of MBI. Finally, we will utilize these exploratory learnings and patterns (combinations of variables and factors) to design and assess the fit of latent class models that would be consistent with causal relationships between clinical characteristics and neuropathological changes to influence development, nature, and progression of NPS in MBI.

Experimental Designs and Methods:

The AZSAND cohort is an ongoing cohort study, in which participants undergo in-depth longitudinal clinical assessments, including measures of cognition, mood, NPS/behavior and function; neurologic exams, and donate their brain for autopsy. The MBI+ population will be defined by the following: 1.) cognitively unimpaired or mild cognitive impairment at death based on consensus criteria AND 2.) ≥ 2 consecutive positive scores on the NPI-Q (2). Adjusting for multiple variables, including age, sex, education, and cognitive performance, we will analyze group differences between MBI+ and MBI- with respect to various neuropathologic changes, including markers of AD, Lewy Body disease, and vascular disease. A sequence of advanced mathematical modeling, analyses and ML algorithms will allow achievement of the aims of this proposal and inform building latent class models that can inform causal relationships to aid characterization and early recognition and risk stratification of NPS associated with neuropathological changes, and for identifying and measuring response to interventions and treatments and emerging experimental therapies.

Proposed One-Year and Long-Term Outcomes:

During the grant period, we consider that completion of Aims 1 and 2a would be excellent progress. If accomplished faster than expected, we will pursue Aims 2b-c. **Findings from the proposed project will be presented in at least one scientific conferences and submitted for a peer-reviewed manuscript.** A long-term goal of this project is to complete similar analyses using data from the Arizona Alzheimer's Disease Core -Brain Imaging and Fluid Biomarkers (BI-FB) Core. As well, we will analyze the temporal sequence of changes in neuroimaging, fluid biomarkers, and NPS. We plan to adapt the machine learning and latent class models to validate findings by using other large datasets, particularly the National Alzheimer's Coordinating Center Uniform Dataset (NACC UDS). We hope that based on our finding, in the future we can develop one or more clinical trials aimed at changing the trajectory of disease in the MBI population.

Year End Progress Summary:

Data Summary

During this funding period, we identified 125 BBDP subjects meeting inclusion criteria. Combining clinical and neuropathologic data, a total of 35 variable were considered as potential features for predicting MBI with 7 clinical and 28 neuropathologic features. Clinical factors included sex, gender, education, age at death, MCI diagnosis, last MMSE before death, and APOE4 carrier status. Neuropathologic factors included various measures of AD, LDB, and vascular disease.

Planned Statistical Analysis

For this hypothesis-establishing study, we first examined the relationship between MBI (categorized as yes or no) and each of the demographic factors and neuropathologic measures including APOE4 carrier status and neuropathologic findings of amyloid plaques, tau tangles, white matter disease, and cerebral amyloid angiopathy. If a given measure was continuous (with age as an example), we used the non-parametric Kruskal-Wallis test, the counterpart of the parametric one-way ANOVA. If a given measure was categorical (such as sex) with less than or equal to six categories, we used the Chi-square test for [distributional] proportion differences. All statistical analyses were carried out using Statistical toolbox and our own codes in MATLAB. This practice aimed to identified those that had close and significant relationship with MBI. At two-tailed $p=0.05$ level and without the correction for multiple comparisons, we identified sex ($p=0.028$) and hippocampal tangles ($p=0.005$) was each significantly associated with MBI. Temporal tangles ($p=0.097$) and hippocampal plaques (0.166) trended toward significant.

Exploratory Analysis Using Machine Learning Techniques

Although the results from the available BBDP data did not single out the key driver(s) for MBI, we believe the proper integration of information over all the measures may provide a better classification power though each measure is not adequate to do so. We explored various machine ML techniques including feature ranking algorithms such as relevant vector regression, partial least square, ensemble regression, SVM (support vector machine), Gaussian Process Regression, and especially the fully connected artificial neural network (ANN) to combine the information from all measures to collectively assess the rate of decline. For this purpose, we randomly divided the entire dataset as 70%, 15% and 15% as training, validation and testing sub-datasets. The most robust model of neuropathologic factors predictive of MBI came from ANN of two-layer topology structures with ten-fold cross-validation which demonstrated R^2 of 0.425 ($p=2.01e-13$).

We also determined the relative importance of each of the 35 clinicopathologic variables, as defined as percentage contribution to the prediction of MBI based on ANN. Twelve variables contributed to most of the importance, which included in descending order of importance (frontal tangles, parietal plaques, frontal white matter changes, sex, occipital CAA, temporal CAA, cortical microinfarcts, total plaques, temporal tangles, parietal CAA, total CAA).

Challenges and Future Plans

A primary challenge in this study was the learning curve of machine learning techniques, and we were fortunate for the large contribution of Dr. Chen. The next steps would be to run the ANN analysis using only these 12 variables as well as to validate this approach to make clinical predictions in a larger dataset, namely NACC UDS data. In summary, very good overall progress was made on assessing and achieving the aims of this grant. The results will be submitted for scientific presentations in conferences in 2022/23 and, as analyses are finalized, preparation and submission of a manuscript is planned for 2023.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Motor Trajectories in neuropathologically-confirmed Lewy Body Disease and other Alzheimer disease and related disorders (ADRD). Parichita Choudhury, MD, Nan Zhang, Msc, Kewei Chen, PhD, Danielle Goldfarb, MD, David Shprecher, DO, Thomas G. Beach, MD, PhD, Charles H. Adler, MD, PhD, Alireza Atri, MD, PhD. Banner Sun Health Research Institute; Mayo Clinic College of Medicine; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background and Significance:

Parkinson's Disease Dementia (PDD) shares several clinical and pathological features[1] and is the second most common misdiagnosis for Dementia with Lewy Bodies (DLB) after Alzheimer's Disease (AD)[2]. Parkinsonism is a core feature of both PDD and DLB[3] but the diagnosis is dependent on the timing of emergence of motor symptoms relative to cognitive symptoms with an arbitrary 1-year cut off[4]. However, lower diagnostic accuracy of DLB antemortem has been associated with absence of parkinsonism[5] and higher Braak stages of comorbid AD pathologically[2,6]. Limited information is available about the characteristics and evolution of parkinsonian motor features in PDD and DLB[7,8]. Compared to PDD, motor features in DLB are considered less likely to be associated with rest tremor[9], to be less severe overall, and to have lower response rates to levodopa[10,11]. Other studies have described the value of recognizing prodromal motor changes prior to development of either Parkinson's Disease or DLB[12,13]. Characterizing the trajectories of extrapyramidal symptoms and signs will be foundational for early recognition of motor subtypes in DLB, providing better prognostication of clinical progression for patients and families, and for identifying and measuring response to experimental interventions and treatments, including emerging disease modifying therapies.

Specific Aims:

Aim 1:

- a) To delineate the motor trajectories (as defined by total UPDRS-II and UPDRS III scores in 'OFF' states) in pathologically confirmed DLB, PDD and Alzheimer Disease cohorts using mixed models for repeated measures (MMRM) multivariate methods.
- b) Using cluster-, latent class- and related mathematical analyses to explore whether the existence of a combination of clinical features, demographic characteristics and motor subtypes (defined by parkinsonian signs, symptoms, or other motor features) can predict the nature and rate of progression of motor trajectories in pathologic cohorts of PDD, and DLB.

Aim 2:

To determine the correlation between topographical distribution and burden of neuropathological changes (such as Unified Lewy body staging system[14], Braak Stages) and nature of motor impairments (defined by variables such as UPDRS and Hoehn Yahr stages) in DLB, PDD and other neurodegenerative conditions.

Preliminary Data:

Over 1435 participant-years of longitudinal data is available for analysis in this project. Preliminary non-linear and piecewise linear MMRM modeling analyses showed that baseline UPDRS-II and UPDRS-III scores were highest ($p < 0.001$) for PDD (mean \pm SE: 14.3 ± 0.78 and 27.4 ± 1.64), followed by DLB with Parkinsonism (5.0 ± 1.05 and 17.4 ± 3.10), DLB without Parkinsonism (3.7 ± 2.54 and 3.8 ± 1.35) and AD (3.2 ± 0.88 and 8.0 ± 1.94). These preliminary analyses suggest that for comparable baseline UPDRS scores, DLB subjects with parkinsonism show a more rapid increase in motor signs compared to PDD.

Experimental Designs and Methods:

Data for this project will be derived from participants of the Arizona study of Aging and Neurodegenerative disorders (AZSAND). Subject cohorts will be selected if they have a final diagnosis of Dementia, two or more movement assessments and a clinicopathological diagnosis of DLB, PDD or AD. To assess between group differences in motor trajectories (defined by UPDRS-II and UPDRS-III) over time from first movement exam, mixed non-linear, MMRM models with random intercept and random slope will be employed. Baseline UPDRS scores (II and III), age, gender, education (years), and time squared (quadratic term) will be accounted for as covariates in the models. To adjust for baseline differences, the interaction term between initial UPDRS-II (when modelling UPDRS-III and vice versa) and time will be introduced as fixed effects. Dependent variables will be subsequent UPDRS II and III scores for each patient. The most non-significant terms will then be removed by backward-elimination.

Proposed One-Year and Long-Term Outcomes:

1. Created defined clinical data sets including cognitive scales, movement exams and pathological confirmation for different cognitive behavioral syndromes and underlying pathological entities.
2. Delineate predicted motor trajectories in Lewy body disease and other neurodegenerative conditions and complete statistical analyses.
3. Submitted at least 2 Abstracts and one peer-reviewed manuscript.

Our Long-term goals are as follows:

1. Apply further causal modelling (Latent Class/Growth Curve models) and machine learning algorithms to better understand causal relationships between neuropathological changes and motor outcomes, and to predict clinical trajectories based on clinical as well as neuropathological characteristics.
2. Validation of proposed models using external data sets (NACC Uniform Dataset).

Year End Progress Summary:

For Aim 1, we focused on Lewy body dementias. We have extracted and defined a clinical data set for longitudinal modelling of motor trajectories in clinicopathological groups with Lewy body dementias. We have also created a defined similar data set for cognitive trajectories in pathological groups of AD, AD with Lewy bodies and dementia with Lewy bodies. To further Aim 1 (specifically Aim 1b) a new career investigator award was applied for (see below). Data analysis using non-linear mixed modelling for UPDRS-II and III, as well as sub-scores were completed as outlined in our short-term goals. In our clinicopathologically defined cohorts of DLB with and without parkinsonism, PDD and Alzheimer's Disease (AD), participants with DLB who exhibited parkinsonism progressed more rapidly compared to all other groups including PDD. These differences in motor trajectories were primarily driven by changes in gait and limb bradykinesia.

For Aim 2, we used simple ANOVAs to understand the correlation between co-pathology in our cohort as an initial step. Our data shows that co-pathology with AD was common in those with DLB, with a greater propensity for higher Braak stages. Further, no differences were noted between PDD participants with and without AD co-pathology and were therefore, combined for the purposes of analysis. Participants with DLB+ Park were more likely to have Unified Lewy body stage IV (84.8%) compared with PDD (63.3%) and DLB- at 60% ($p < 0.001$). On the other hand, cases with PDD and DLB- Park had higher frequency of Unified LB Stage III diagnosis (30.6% and 40% respectively, as opposed to DLB+ Park (15.2%, $p < 0.0001$).

Abstracts reporting the results of the motor trajectories in Lewy body dementias were presented at Alzheimer's Association International Conference [15] (Denver, 2021 and upcoming at San Diego, 2022) and International Lewy Body Conference, 2022 (NewCastle, United Kingdom) as

posters. A manuscript with the data is currently being reviewed by co-authors and will be submitted to Alzheimer's and Dementia journal for further review. The data also was presented (oral) at the scientific meeting for Lewy Body Dementia Professional Interest Area for ISTAART (International Society to Advance Alzheimer's Research and Treatment) in September, 2021.

Two further grants were applied for stemming from this data set. A Lewy body dementia association (LBDA) mentorship grant (\$4000 award amount) was applied for and received to define the cognitive trajectories of AD, DLB, PDD and AD with Lewy bodies. This has furthered collaboration with LBDA and Mayo Clinic, Rochester (Brad Boeve, MD is mentor for this grant). Furthermore, a new career investigator award from LBDA (\$50,000 award amount) was submitted to utilize machine learning technique to predict Lewy body pathology with a composite risk score. This will further the proposed long-term outcomes outlined in this initial grant.

References:

- [1] Sezgin M, Bilgic B, Tinaz S, Emre M. Parkinson's Disease Dementia and Lewy Body Disease. *Semin Neurol* 2019;39:274–82. <https://doi.org/10.1055/s-0039-1678579>.
- [2] Rizzo G, Arcuti S, Copetti M, Alessandria M, Savica R, Fontana A, et al. Accuracy of clinical diagnosis of dementia with Lewy bodies: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2018;89:358–66. <https://doi.org/10.1136/jnnp-2017-316844>.
- [3] Shoeibi A, Litvan I, Juncos JL, Bordelon Y, Riley D, Standaert D, et al. Are the International Parkinson disease and Movement Disorder Society progressive supranuclear palsy (IPMDS-PSP) diagnostic criteria accurate enough to differentiate common PSP phenotypes? *Park Relat Disord* 2019;69:34–9. <https://doi.org/10.1016/j.parkreldis.2019.10.012>.
- [4] McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor J-P, Weintraub D, et al. Diagnosis and management of dementia with Lewy bodies. *Neurology* 2017;89:88–100. <https://doi.org/10.1212/WNL.0000000000004058>.
- [5] McKeith IG, Ballard CG, Perry RH, Ince PG, O'Brien JT, Neill D, et al. Prospective validation of Consensus criteria for the diagnosis of dementia with Lewy bodies. *Neurology* 2000;54:1050–8. <https://doi.org/10.1212/WNL.54.5.1050>.
- [6] Ferman TJ, Aoki N, Boeve BF, Aakre JA, Kantarci K, Graff-Radford J, et al. Subtypes of dementia with Lewy bodies are associated with α -synuclein and tau distribution. *Neurology* 2020;95:E155–65. <https://doi.org/10.1212/WNL.0000000000009763>.
- [7] Burn DJ, Rowan EN, Minett T, Sanders J, Myint P, Richardson J, et al. Extrapyrimal features in Parkinson's disease with and without dementia and dementia with Lewy bodies: A cross-sectional comparative study. *Mov Disord* 2003;18:884–9. <https://doi.org/10.1002/mds.10455>.
- [8] Ballard C, O'Brien J, Swann A, Neill D, Lantos P, Holmes C, et al. One year follow-up of parkinsonism in dementia with Lewy bodies. *Dement Geriatr Cogn Disord* 2000;11:219–22. <https://doi.org/10.1159/000017240>.
- [9] Onofrij M, Varanese S, Bonanni L, Taylor JP, Antonini A, Valente EM, et al. Cohort study of prevalence and phenomenology of tremor in dementia with Lewy bodies. *J Neurol* 2013;260:1731–42. <https://doi.org/10.1007/s00415-013-6853-y>.
- [10] Taylor JP, McKeith IG, Burn DJ, Boeve BF, Weintraub D, Bamford C, et al. New evidence on the management of Lewy body dementia. *Lancet Neurol* 2020;19:157–69. [https://doi.org/10.1016/S1474-4422\(19\)30153-X](https://doi.org/10.1016/S1474-4422(19)30153-X).
- [11] Boeve BF, Dickson DW, Duda JE, Ferman TJ, Galasko DR, Galvin JE, et al. Arguing against the proposed definition changes of PD. *Mov Disord* 2016;31:1619–22. <https://doi.org/10.1002/mds.26721>.

- [12] Fereshtehnejad S-M, Yao C, Pelletier A, Montplaisir JY, Gagnon J-F, Postuma RB. Evolution of prodromal Parkinson's disease and dementia with Lewy bodies: a prospective study. *Brain* 2019;142:2051–67. <https://doi.org/10.1093/brain/awz111>.
- [13] McKeith IG, Ferman TJ, Thomas AJ, Blanc F, Boeve BF, Fujishiro H, et al. Research criteria for the diagnosis of prodromal dementia with Lewy bodies. *Neurology* 2020;94:743–55. <https://doi.org/10.1212/WNL.00000000000009323>.
- [14] Beach TG, Adler CH, Lue LF, Sue LI, Bachalakuri J, Henry-Watson J, et al. Unified staging system for Lewy body disorders: Correlation with nigrostriatal degeneration, cognitive impairment and motor dysfunction. *Acta Neuropathol* 2009;117:613–34. <https://doi.org/10.1007/s00401-009-0538-8>.
- [15] Choudhury P, Zhang N, Shprecher D, Belden C, Goldfarb D, Shill H, et al. Longitudinal motor decline in dementia with Lewy bodies and Parkinson's disease dementia in a community autopsy cohort. *Alzheimer's Dement* 2021;17:e055838. <https://doi.org/10.1002/ALZ.055838>.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Enhancement of Arizona Alzheimer's Consortium Resource Sharing and Recruitment.
Alireza Atri, MD, PhD, Thomas Beach, MD, PhD, Danelle Goldfarb, MD, Parchita Choudhury, MD. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

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.

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 into Alzheimer's disease (AD) and AD Related Disorders (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. They continue to provide a world-leading scientific resource of longitudinal and neuropathological data, brain and body tissues for the study of AD, Parkinson's disease, and related disorders in their Brain and Body Donation Program (BBDP)—and they have begun to incorporate ante-mortem biomarkers and new brain tissue resources to help researchers address their goals with even greater impact.

Experimental Designs and Methods:

This proposal requests complementary support to enhance ongoing efforts for participant recruitment, data, brain and body tissue collection and resource sharing as part of the Arizona Alzheimer's Consortium ADRC and affiliated programs.

Aim 1:

To support specific efforts to help with ongoing participant recruitment, data, brain and body tissue collection and resource sharing as part of the Arizona Alzheimer's Consortium ADRC and affiliated programs.

To help achieve this aim partial support is requested to:

- a) perform standard evaluations and collect UDS and additional data on all participants, including a large number of Hispanic/Latino and Native American participants.
- b) provide neuropathologic diagnoses and process, store and distribute postmortem brain tissue, including from those who provided blood samples in the last 1-2 years of their lives.
- c) support and provide access to genetics, brain imaging (MRI, amyloid PET, tau PET), cerebrospinal fluid (CSF) and BBBs of AD.

Aim 2:

To forge innovative and impactful multi-institutional, multi-disciplinary collaborations, to provide shared resources, and to collaborate with other institutions to ensure the development of sufficient infrastructure for the rapid enrollment of AD and ADRD studies,

To help achieve this aim partial support is requested to:

- a) support necessary personnel to ensure the development of sufficient infrastructure for rapid enrollment into AD and ADRD studies
- b) Oversee outreach, education, recruitment projects such as the Brain Health Check In and community lectures to facilitate recruitment into studies.

Proposed One-Year and Long-Term Outcomes:

The proposed outcomes would be to provide the shared resources needed to help advance the study, early detection, tracking, diagnosis, treatment and prevention of AD and related dementias, develop new research leaders, help find an AD prevention therapy as soon as possible, and establish the roles of blood-based biomarkers in these endeavors.

This will contribute significantly to the development of shared resources that support AD and ADRD relevant research and will give our researchers a chance to find ways to treat and prevent AD.

Year End Progress Summary:

As manifest by an exemplary record of number of ADRC participants and visits; ongoing studies and clinical trials; publications; grant funding; and AD/ADRD and brain health-related community outreach, education and service programs, the complementary support provided was highly successful to accomplish the aims of this grant during the funding period.

Progress on Aim 1

In support of Aim 1, during the funding period, under the direction of Dr. Alireza Atri, and supported by Dr. Parichita Choudhury and team, we performed 768 standardized ADCC/ADRC clinical research visits at BSHRI; collected NACC UDS cohort and additional visit data; and quality assured and consensus evaluated these assessments; and have 187 active ADRC participants. Under the direction of Dr. Beach, we provided the neuropathologic diagnosis, processed, stored and distributed postmortem brain tissue, and the Neuropathology Core performed 11 autopsies on subjects enrolled in the ADRC Clinical Core. The ADRC Clinical Core cases and their clinical diagnoses were: 2 AD, 6 normal controls, 2 vascular or mixed dementia and 1 dementia, NOS. Over the funding period 187 tissue disbursements were made to researchers, of which 119 involved ADRC subjects.

Under co-direction by Dr. Atri, and supported by Dr. Goldfarb, we continued to support and provide access to genetics, brain imaging (MRI, amyloid PET, tau PET), cerebral spinal fluid (CSF) and blood brain biomarkers of AD. During the reporting period, we acquired scans from 37 participants from the Brain Imaging and Fluid Biomarkers (BIFB) and ADRC efforts; and, over the course of the ADCC BIFB, we have neuroimaging and blood biomarker samples/data for a total of 191 participants who have been scanned and provided blood samples; and CSF samples from 112 participants who underwent lumbar punctures. In fall 2021, the NIA replaced the completed ADCC supplement by expanding the scope of Arizona Disease Research Center (ADRC) to include a Biomarker Core. From 9/21 to 12/21, BSHRI consented 12 participants into the study and 7 completed scanning. From 1/22 through 3/22, BSHRI consented 22 participants and 2 completed scanning.

Progress on Aim 2

In support of Aim 2, we expanded the availability and reach of the Brain Health Check-In (BHCI) program. This free community service, first piloted in December 2018, allows individuals to schedule or drop-in for a 45 minute-1 hour brain health check. After interview assessment and testing our team provides participants with feedback regarding their brain health concern status. Information regarding brain-healthy behaviors and resources available in the community (clinical, support, research) is also provided. Overall, this program, under the direction of Dr. Alireza Atri and Dr. Christine Belden, has provided 738 individuals with free brain health concern status

assessments (222 in 2021-22) along with feedback, information, education, resources and referrals. Over 400 participants have been reached for follow up. Participants in the program continue to rate it very highly with evaluation ratings ranging from 4.5-4.7 out of 5.0 for Satisfaction and also for Likely to Recommend. In 2021-22 reporting period we had 22 referrals to research and 22 referrals to clinic from BHCI.

Our research Trials programs at BSHRI, under the direction of Dr. Atri, Dr. Danielle Goldfarb, and Carolyn Liebsack, RN, made referrals for 661 persons in the 2021-22 reporting period.

Our AD/ADRD diversity, equity and inclusion (DEI) efforts, led by Dr. Danielle Goldfarb, developed a partnership with First Institutional Baptist Church (FIBC), a predominantly Black/African American church in Phoenix to create REAL TALK Dementia/Alzheimer's, which focuses on community partnership, trust and relationship building to improve ADRD knowledge; appreciation of benefits of timely detection, care, prevention strategies, and research participation; and to facilitate access to ADRD care and resources. Through REAL TALK Dementia/AD we reached 235 participants (87% African-American, Hispanic, Asian or Native American). Additionally, on 4/30/22 our Brain Health outreach program at a FIBCO health fair resulted in 18 BHCI's in one day.

Under direction of Dr. Atri and co-supported by Drs. Choudhury and Goldfarb and our BSHRI team, our community and speaker's bureau education lectures reached 473 people in 2021 (207 from 1-4/22); our local/regional continuing education (CE) programs/lectures provided 17 programs to 947 participants, including over 300 participants via the BSHRI AD/ADRD updates one-day CE symposium in 2/22; and the Dementia Untangled education and support podcasts (more than 32 podcasts, including podcast co-host Janice Greeno, and podcasts with Dr. Atri, more info at: <https://podcasts.apple.com/us/podcast/dementia-untangled/id1558126995>) garnered >28,500 downloads.

Finally, supported by a track record of successfully conducting the type of programs that received complementary support by this grant, Drs. Atri and Beach, along with Dr. Geidy Serrano, have been awarded a 3-year Foundation for NIH (FNIH) \$2.8+ million grant (contracting in process) to lead a single-center study based at BSHRI to assess and validate a new PET scan ligand (SV2A PET synaptic ligand) that quantifies the amount of brain synaptic connections in living persons; and BSHRI also just received notice (4/2022) that it will be granted \$150,000 from the national AHEAD AD prevention study diversity grant RFA (Drs. Goldfarb and Atri) which will provide funding for an Alzheimer's prevention nurse navigator to promote greater DEI outreach for AD/ADRD clinical care and research.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Biomarkers in Idiopathic REM Behavior Disorder (iRBD) as a Predictor of Neurodegenerative Disease. Joyce K. Lee-Iannotti, MD, David Shprecher, DO, Charles H. Adler, MD, PhD, Thomas Beach, MD, PhD, Parichita Choudhury, MD, Kewei Chen, PhD. Banner Sleep Center; Banner Sun Health Research Institute; Mayo Clinic College of Medicine; Banner Sun Health Research Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Project Description:

We propose a pilot feasibility biomarker study of idiopathic REM behavior disorder (iRBD). If the biomarkers studied show promise in separating iRBD subjects from controls, they will be worthy of prospective study to better understand, predict, and potentially measure progression from iRBD to α -synucleinopathy. Such research would be critical to the design of trials to identify disease-modifying therapy to slow neurologic deterioration in iRBD, prognosticate for future neurologic complications, and aid in the understanding of the pathophysiologic mechanisms of neurodegenerative disease processes.

Specific Aims:

Specific Aim 1: To develop additional biomarkers for synucleinopathy burden that are currently not being assessed in other registries.

Aim 1a. To determine if abnormal α -synuclein aggregates can be detected by skin biopsy in patients with iRBD as a potential biomarker for impending synucleinopathy. Studies have shown potential use for this method in detecting phosphorylated α -synuclein (p- α -syn) deposits within dermal nerves as a sensitive and specific way to discriminate patients with PD from healthy controls.

Hypothesis 1: Skin biopsies for p- α -syn can clearly and statistically significantly separate iRBD subjects from neurologically healthy controls.

Aim 1b. To determine if serum neurofilament light chain (NfL), a marker for axonal damage is a biomarker for Parkinson's Disease progression in iRBD patients. Mollenhauer et al demonstrated that NfL levels in blood samples were increased in PD subjects compared in healthy controls, increased significantly over time in Parkinson's patients, and correlated with a clinical measure of disease severity. (2) NfL could serve as the first fluid biomarker for PD in iRBD patients.

Hypothesis 2: Serum NfL will be sensitive and specific in separating iRBD from neurologically healthy control subjects.

Background and Significance:

Rapid eye movement (REM) sleep behavior disorder (RBD) is a unique parasomnia characterized by a lack of motor inhibition during REM sleep leading to potentially harmful dream-enacting behaviors. (3) Idiopathic RBD (iRBD) without any secondary cause is strongly associated with later development of α -synucleinopathies including PD, DLB and MSA, often preceding neurological manifestations by several years to decades. (4) Phenoconversion risk is approximately 20-50% within 5 years of RBD symptom onset, rises to 50-75% in 5-10 years, and 80-92% in long-term follow-up. (5,6-11) Therefore, RBD is an indicator of presymptomatic neurodegeneration. Several biomarkers have been identified as sensitive but not specific for Parkinson's disease in iRBD including quantitative changes in olfaction (4), abnormal quantitative

motor testing, color vision abnormalities, severe constipation, and abnormal DAT SPECT scans. (7,8) More sensitive prodromal markers of impending conversion are needed.

Preliminary Data:

More recently, skin biopsy has emerged as a promising and less invasive biomarker. (9) One study using biopsies of multiple unilateral sites (C7 paraspinal area, T10 paraspinal area, and proximal and distal leg) showed phosphorylated α -synuclein positivity in 10 (56%) of 18 patients with isolated RBD, 20 (80%) of 25 patients with early Parkinson's disease, and 0 of 20 controls. (9) A more recent study of a single biopsy from a C8 cervical paravertebral site using an automated immunohistochemical assay showed phosphorylated α -synuclein in 23 (82%) of 28 patients with isolated RBD. (11) These studies have shown a combined specificity of 100% and a sensitivity of 58–87%.

Experimental Designs and Methods:

Specific Aim 1a: At least 20 iRBD BBDP participants and 20 controls (participants without RBD) will be provided with the skin biopsy at Banner Sun Health Research Institute (BSHRI). We plan to recruit age and gender matched controls from caregivers of patients in the BSHRI memory and movement disorders clinic. Punch biopsies of the skin will be obtained by study clinicians under local anesthesia (lidocaine), in standardized locations – two biopsies from the bilateral paravertebral regions at the C8 level 3- cm from the midline (2).

Specific Aim 1b: At least 10 iRBD BBDP participants will be enrolled for serum neurofilament light chain testing with analysis anticipated by the Simoa NF-light assay kit. (2) Controls will be age and gender matched controls from the BBDP database. This assay is a digital immunoassay for the quantitative determination of NfL in serum, plasma, and cerebrospinal fluid (CSF).

Proposed One-Year and Long-Term Outcomes:

This project is a pilot feasibility study of identifying two novel biomarkers that would separate idiopathic REM sleep behavior disorder (iRBD) subjects from neurologically healthy controls and better understand, predict, and potentially measure progression from iRBD to an α -synucleinopathy (Parkinson's disease, multiple system atrophy or diffuse Lewy Body dementia). The two biomarkers proposed include 1) α -synuclein aggregates detected by skin biopsies and identified through immunohistochemical staining techniques and 2) serum neurofilament light chain (NfL). If promising, this study could serve as the basis for future, more extensive studies to assess the relevance of identifying a cohort of subjects at highest risk for neurodegenerative disease for disease-modifying treatment studies.

Year End Progress Summary:

Specific Aim 1a: Since 7/1/2021, a total of 4 patients were enrolled. One patient was excluded due to his PSG findings confirming secondary RBD related to untreated sleep apnea, rather than idiopathic RBD. This was discovered post-specimen collection and entered as a protocol deviation and the patient was immediately notified. Skin biopsy findings and reports are pending but currently being analyzed.

Over the course of the project, we met monthly with the investigators of the Arizona Study of Neurodegenerative Disease and Aging who follow the participants consented for tissue donation in the Brain and Body Donation Program (BBDP) at BSHRI. This has included multiple collaborations to study skin and fluid biomarkers in predicting the manifestation of neurodegenerative disease. Up until the funding period, only participants with neurodegenerative disease, cancer, or healthy controls had been enrolled; no individuals with polysomnogram confirmed RBD had been enrolled. The four individuals enrolled in this pilot study were co-

enrolled in the BBDP. This pilot study established a formal protocol whereby individuals with RBD will be recruited into BBDP, have their diagnosis confirmed by a sleep expert, and have important tissue and fluid biomarkers collected during life. As RBD is a prodromal state for synucleinopathy, these biomarkers will guide design of neurodegenerative disease prevention studies. More importantly, whole body tissues collected from participants will guide research about pathophysiology of synucleinopathy.

Specific Aim 1b: Similar to Aim 1a, 4 patients were enrolled. One patient was excluded due to his PSG findings confirming secondary RBD related to untreated sleep apnea, rather than idiopathic RBD. This was discovered post-specimen collection and entered as a protocol deviation and the patient was immediately notified. The serum/plasma samples will be safely stored until a batch can be delivered to Quanterix for processing.

Recruitment into this study was challenging. Approximately 150 participants were contacted via phone calls but found to 1) not have PSG confirmed RBD features so excluded, 2) declined due to the concerns of the skin biopsy procedure, and/or 3) residing out of state.

In prior less invasive RBD research (which involved comparing a wearable home device to the full sleep study array), we had been more successful in recruitment, largely through the use by newspaper advertisements. However, for reasons that remain to be elucidated; similar advertisements in the same venues were not effective during the COVID-19 pandemic. The main pool of eligible participants came from the sleep center patient population. Though we identified over 600 through an electronic medical records search, our staff did not have bandwidth to contact all of them. We have therefore arranged with our additional funding for the MJFF PPMI study to fund a student intern whose sole responsibility will be to make patient calls to schedule conversations with our recruitment manager and/or study coordinator about research on links between sleep and brain health. We are now finalizing a contract to provide continued time and effort funding for our PI (JLI) and necessary support staff to ensure successful ongoing recruitment.

Reference List:

1. Antelmi, E, Donadio V, et al. Skin nerve phosphorylated α -synuclein deposits in idiopathic REM sleep behavior disorder. *Neurology* 2017;88:2128-2131.
2. Mollenhauer B, Dakna M, et al. Cross-sectional and Longitudinal Validation of Serum Neurofilament Light Chain (NfL) as a Biomarker of Parkinson's Disease Progression. Sep.11,2019; doi:<http://dx.doi.org/10.1101/762237>.
3. Schenck CH, Mahowald MW. REM sleep behavior disorder: clinical, developmental, and neuroscience perspectives 16 years after its formal identification in SLEEP. *Sleep* 2002;25(2):120-138.
4. Boeve B, Silber M, et al. Association of REM sleep behavior disorder and neurodegenerative disease may reflect an underlying synucleinopathy. *Mov Disord.* 2001;16:622-630.
5. Postuma RB, Montplaisir J. Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder. *Neurology.* 2009;72(15)1296-1300.
6. Fantini ML, Postuma RB, Montplaisir J, et al. Olfactory deficit in idiopathic rapid eye movement sleep behavior disorder. *Brain Res Bull.* 2006;70(4-6):386-390.
7. Iranzo, A, Lomena F, Stockner H, et al. Decreased striatal dopamine transporter uptake and substantia nigra hyperchogenicity as risk markers of synucleinopathy in patients with idiopathic rapid-eye movement sleep behavior disorder: a prospective study. *Lancet Neurol.* 2010;9(11):1070-1077.

8. Postuma, R, Iranzo, A , et al. Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study. *BRAIN* 2019;142:744-759.
9. Zitser J, Gibbons C, Miglis MG. The role of tissue biopsy as a biomarker in REM sleep behavior disorder. *Sleep Med Rev* 2020; 51: 101283. [PubMed: 32187564].
10. Doppler K, Jentschke HM, Schulmeyer L, et al. Dermal phospho-alpha-synuclein deposits confirm REM sleep behaviour disorder as prodromal Parkinson's disease. *Acta Neuropathol* 2017; 133: 535–45. [PubMed: 28180961].
11. Al-Qassabi A, Tsao TS, Racolta A, et al. Immunohistochemical detection of synuclein pathology in skin in idiopathic rapid eye movement sleep behavior disorder and parkinsonism. *Mov Disord* 2021; 36: 895–904. [PubMed: 33232556].
12. Goetz, CG, Tilley BC, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord* 2008; 23: 2129-70.

**BARROW NEUROLOGICAL INSTITUTE
PROJECT PROGRESS REPORTS**

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Single cell profiling of blood-brain and blood-CSF barriers in dementias. Nadine Bakkar, PhD, Kendall Van Keuren-Jensen, PhD. Barrow Neurological Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

- 1) Specific Aim 1: Single cell analysis of brain microvasculature in dementias
- 2) Specific Aim 2: Single cell analysis of the choroid plexus in dementias

Background and Significance:

Vascular dysfunction is a well-accepted feature of Alzheimer's disease (AD) that manifests itself with both structural and functional vascular changes. Yet, very little is known about the global alterations in endothelial cells in human AD, despite the current widespread use of single cell sequencing technologies due to their low abundance relative to other brain cells. Recent publications have proposed methods to enrich for endothelial cells in frozen postmortem human cortex. Using these techniques, we proposed to investigate the blood brain barrier (BBB) in dementias. We also proposed to develop a protocol for investigate the blood-CSF barrier (BCSFB) in dementias. The BBB and BCSFB being at the interface between the blood and the CSF, are key for bridging systemic drug delivery and direct access to the CNS. However, a better understanding of the healthy BBB and BCSFB in humans, the relative contribution and molecular signature of individual components of these barriers along with the changes that occur in dementias is required to identify potential therapeutic opportunities.

Preliminary Data, Experimental Design and Methods:

We have previously published a global transcriptomic analysis by RNA-Seq on the BCSFB in ALS and non-neurological controls and unveiled global disruptions in junctional markers, inflammation, as well as vascular disruptions (Saul et al.2020. Acta Neuropathol Commun). We have extended our study to a focused investigation of neuroinflammation in AD, FTD, ALS-FTD and control postmortem choroid plexus samples using a Nanostring technology. Although both methods have their advantages, bulk RNA transcriptomics masks the relative contribution of individual cell types to the global transcriptomic signature and hides potentially meaningful gene regulation within specific cells.

To perform an analysis of the BBB in dementias for Aim 1, we first propose to enrich for endothelial cells by relying on the physical properties of these cells that are entombed in vessel basement membranes. We will use age and gender-matched human postmortem frozen frontal cortex tissues of LBD, FTD and controls obtained from various brain banks. Endothelial enriched nuclei will be isolated, nuclei-specific libraries prepared using 10x Genomics and sequenced using Illumina NovaSeq technologies at Tgen. Data will be analyzed to identify fold changes in different cell types across the groups. For Aim 2, we will use frozen postmortem choroid plexus tissues available in-house, as well as obtained from the UCSF neurodegenerative disease brain bank. We will optimize a protocol that combines the endothelial enrichment steps developed in Aim 1 along with published protocols, isolate nuclei, construct 10x Genomics libraries and sequence those nuclei. Again, data will be analyzed and differentially expressed genes in the various cell types will be compared across groups analyzed.

Proposed One-Year and Long-Term Outcomes:

Data generated from this project will shed the light onto potential inherent commonalities and differences in the BBB and BCSFB of AD, FTD and LBD compared to controls, and identify cell-

specific changes. Given the unique role of the BCSFB and BBB as a gate into the CNS, this will in turn help with development of better drug delivery routes for neurodegenerative diseases. This analysis generates a lot of data on changes across multiple cell types relevant for dementias and can generate information on various pathways altered, with the potential to provide preliminary data for several downstream projects. As a junior investigator, this grant will thus help generate preliminary data to apply for larger national multi-year grants to further my scientific career.

Year End Progress Summary:

Aim 1. Using AAC funds, we have optimized the protocol to enrich for endothelial cells and collect intact nuclei from postmortem frozen frontal cortex. We have performed multiple iterations of the extraction and have finalized a protocol that yields endothelial-enriched fraction of nuclei suitable for single nuclear RNA-seq following multiple steps of manual dounce homogenization, spin on a Dextran gradient to remove the myelin, and then collecting the blood vessel pellets. Blood vessel pellets are subsequently ruptured on top of a cell strainer to release endothelial and endothelial-associated nuclei (pericytes, smooth muscle cells, astrocytes, microglia) before processing them through the single nuclei library prep and sequencing. Tissues requested needed to pass stringent selection criteria of PMI (postmortem interval), no known genetic alterations, detailed accompanying clinical documentation, as well as be age and gender-matched.

Tissue procurement from three different postmortem brain banks proved a time-consuming challenge at the MTA level (locally and elsewhere), as well as the tissue bank level (one brain bank is finally now shipping out samples requested in September 2021). We couldn't find a brain bank to fulfill the request for LBD tissues and we had to drop this group. We are now ready to perform the experiment with all the tissues being on-site, and are planning to compare four groups of 5 samples each: Controls, bvFTD-TDP, and C9orf72-FTD, and C9orf72-ALS-FTD. Once samples are sequenced, cell types within the different groups will be analyzed and compared to data on the AD group generated from Yang et al (2021). Differentially expressed genes and pathways within endothelial and endothelial-associated cells will be generated to identify general dementia-mediated alterations in the brain microvasculature as well as changes specific to one dementia vs the other.

Aim 2. We adapted a protocol from Yang et al. 2020 for single nuclei isolation from frozen choroid plexus (CP) tissues and improved it to enrich for endothelial cells. Our optimized protocol produces a yield of around 15,000 nuclei per 50mg of starting material, with four-fold enrichment in endothelial cell markers compared to published protocols. We had initially proposed to compare 4 groups, consisting of controls, FTD, LBD and AD with four subjects each. To ensure good quality single nuclear RNA-seq data, we had strict restrictions for CP tissue location (lateral ventricle), PMI interval, and available accompanying clinical data. We have however faced a challenge with obtaining frozen CP tissues from the proposed groups. We were unable to find a brain bank that could fulfill the request and provide good quality frozen CP from the LBD and AD groups. The reason being that this brain region is not one routinely harvested or collected in brain banks. To remedy this limitation, we have re-structured the experimental groups to compare and are examining 5 controls, 5 FTD, 5 fast progressing ALS and 5 slow-progressing ALS. These tissues were obtained from the local Target ALS branch at BNI and processed through our snRNA-seq pipeline. Briefly, tissues were homogenized using a Dounce homogenizer and nuclei were extracted and isolated using the fluorescence activated cell sorter (FACS) at Tgen to select for intact nuclei. Libraries from the isolated nuclei were constructed following the 10x Genomics protocol and submitted for sequencing using Illumina NovoSeq methodologies. We are currently waiting to get the results from the sequencing analyzed to identify cell types and differentially regulated genes and pathways.

Methods developed in this grant were used as preliminary data for an R21 submission to NIH/NIA proposing to use the same techniques to compare and contrast the BBB and BCSFB within individual patients. That grant got a favorable fundable score, and we are waiting on the council meeting in September 2022 to hear about their decision whether to fund it. We have also fostered our collaboration with Dr Kendall Van-Keuren Jensen's laboratory, a collaboration that will extend beyond this grant to further ones, including the R21 if funded.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Tau, Splicing and RNA expression in the Default-Mode Network in DS. Sylvia E. Perez, PhD, Kendall Van Keuren-Jensen, PhD. Barrow Neurological Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

The goal of this proposal is to elucidate the molecular events associated with the death of projection pyramidal neurons in the Frontal Cortex (FC) and Precuneus (PreC), two cortical areas involved in learning and memory, and part of the Default Mode Network (DMN), which is dysfunctional in both Down syndrome (DS) and Alzheimer's disease (AD). We previously reported that the number of neurofibrillary tangles, a type of neuronal lesion containing the protein tau and associated with cellular death and dementia, and present also in AD patients, was greater and more advanced in the FC of demented DS (DSD+) than DS without dementia (DSD-). Our preliminary data show that RNA splicing, a key process in gene expression and protein formation, including tau, is compromised in DSD+. So, in this proposal we are testing that aberrant mRNA splicing, causes an increase in the number of NFTs in the FC and PreC in DSD+ compared to DSD-. This is relevant from a basic science, translational, and clinical perspective, as survival of the projection neurons in FC and PreC are critical for maintenance of the memory circuits in both, AD and DS.

Aim 1: We hypothesize that during the progression of tau pathology and mislocalization of U1-70K alterations of select transcripts related to tau dysfunction and nuclear splicing within FC layer V pyramidal neurons will be greater in DSD+ compared to DSD- and PreC.

Aim 2: We hypothesize that gene expression alterations related to tau pathology and nuclear splicing within in the FC will be greater in DSD+ compared DSD-, and the PreC using RNA sequencing.

Background and Significance, Preliminary Data, Experimental Design and Methods:

Unlike AD, treatment approaches failed to show any efficacy to treat dementia in DS. Recently, the AD and DS fields have intensified the investigation of the role of tau, a microtubule-associated protein, as a treatment approach for AD and DS. Interestingly, tau RNA is spliced, generating 3Rtau and 4Rtau isoforms in same proportions, and its imbalance was associated with NFT formation and dementia. The discovery that abnormal splicing of tau exon 10 caused neurodegeneration linked to NFT formation in frontotemporal dementia, established a molecular link between tau splicing and tauopathies, including DS and AD. Recent studies demonstrated an aberrant extranuclear mislocalization of the crucial splicing U1-70K and U1A nuclear ribonucleoproteins (RNP) proteins in the form of insoluble NFTs in AD and DS.

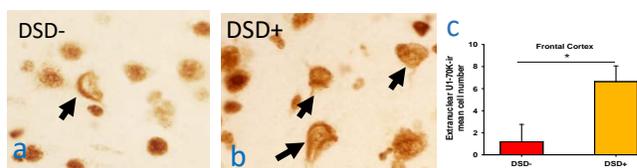


Figure 1. (a, b) Photos showing cytoplasmic mislocalized U1-70k positive NFTs (arrows) in FC layer V neurons in DSD+ and DSD-, respectively. (c), U1-70k NFTs were significantly higher in DSD+ (n=5) compared to DSD- (n=5). $P < 0.05$. Scale bar = 25 μm .

Our group revealed that mislocalized U1-70K within NFTs were also observed in DSD- (**Fig. 1**). We show significant increase in the number of FC projection neurons bearing mislocalized U1-70K in layer V in DSD+ compared to DSD- (**Fig. 1**), which co-localized with the early phosphorylated (pSer²⁰²/The²⁰⁵) AT8 and

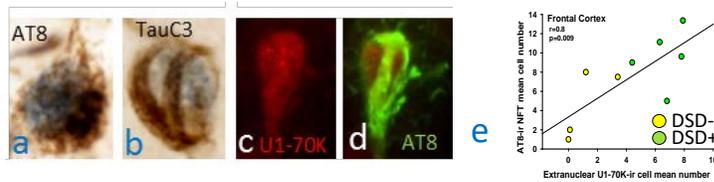


Figure 2. Nuclear and NFT positive U1-70K (blue) co-localizes with (a) AT8 (brown) and (b) TauC3 (brown) in DSD+. Immunofluorescence showing the colocalization of U1-70K (c, red) with AT8 (d, green). (e) shows a positive correlation between the numbers of AT8 immunoreactive (-ir) NFTs and extranuclear U1-70K-ir neurons in the FC layer V across the two groups. $p < 0.05$

dysregulation to NFT pathogenesis (Fig. 2). Moreover, our preliminary Nanostring data show a dysregulation in the expression of several splicing and transcription-related genes in FC between DSD+ and DSD- [e.g., CLK1, a serine-arginine kinase CLK1 involved in alternative splicing; MNAT1 gene: an assembly factor of the CDK-activating kinase, which is involved in transcription activation; TAF4 and TAF9, TATA-box binding protein-associated factors 4 and 9, respectively, both involved in transcription activation by RNA polymerase II] (Fig. 3). We found a significant upregulation of CLK1 expression in FC and PreC cortex in DSD+ compared to DSD-, which was strongly associated with 4R/3Rtau transcript values in the FC, but weaker in PreC in DS. The latter show lesser 3Rtau+4Rtau expression than FC (Figs. 3 and 4), revealing a differential spliceosome dysfunction between these two DMN hubs in DS. We provide novel evidence that tau splicing is compromised in DSD+ and perhaps plays a critical role in the onset of advanced

late truncated (Asp⁴²¹) TauC3 tau markers in DS FC pyramidal neurons (Fig. 2). Moreover, our findings demonstrated a significant positive correlation between the number of FC projection neurons bearing extranuclear U1-70K-NFTs and number of FC AT8 positive NFTs in layer V-VI, but not FC plaque load in DS, linking U1-70K

tau pathology seen in the FC in DSD+. The proposed experiments will provide seminal information aimed at understanding the role(s) of nuclear splicing and tau epitopes and mechanisms involved in the selective vulnerability of projection neurons in the FC and PreC in DS. These findings will aid in the development of novel therapies to treat dementia in DS with translation to AD.

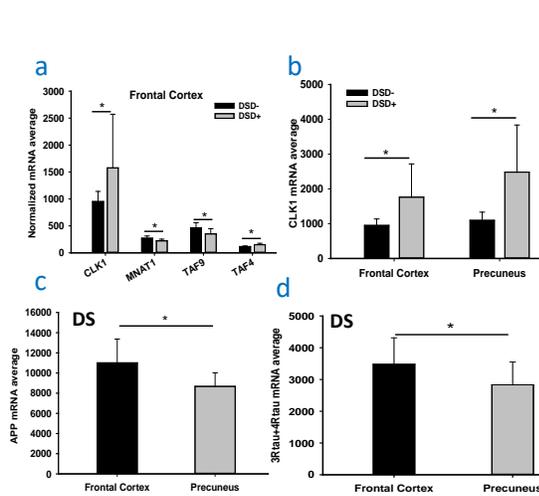


Figure 3. FC Nanostring data showing differential gene expression for several splicing and transcription factors between DSD+ and DSD-, including CLK1 (a). CLK1 mRNA expression was significantly increased in FC as well as in PreC in DSD+ compared to DSD- (b). A significant upregulation in APP (c) and 3R+4Rtau (d) transcripts was observed in the FC compared to PreC in DS indicative of higher AD-like pathology in FC than in PreC in DS. $*p < 0.05$.

Aim1. We will test the

hypothesis FC NFTs bearing early and late tau epitopes and mislocalized U1-70K splicing proteins display a greater downregulation of classes of genes related to the spliceosome, cell death, cell signaling and tau pathology in DSD+ vs DSD- and PreC. Single population expression profiling combined with custom-designed microarray analysis will be applied to tissue according to our previously published protocols. Here, double (U1-70K+AT8 and U1-70K+TauC3, and single

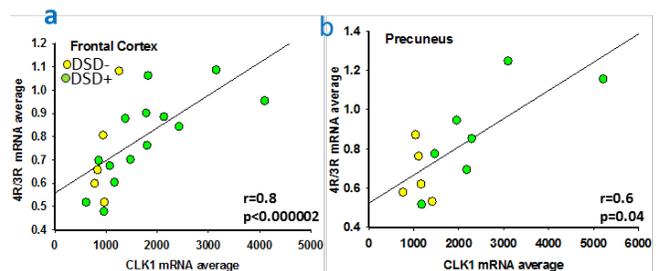


Figure 4. FC CLK1 gene expression shows a positive correlation with 4R/3Rtau expression in the FC (a), but weakly within PreC across the DS groups (b).

non-tangle-bearing nuclear U1-70K will be micro-aspirated using a Zeiss laser capture microscope (LCM), mRNA will be extracted, amplified, and evaluated using custom-designed microarrays. Approximately 100 individual labeled cells will be micro-dissected via LCM per reaction/per case as we described in DS. Experiments are run in triplicate and blinded, and RNA profiling will be validated using qPCR and/or protein expression. RIN values will be used to determine the quality of the RNA. Relative changes in total hybridization signal intensity and individual mRNAs are analyzed using one-way ANOVA and adjusted for false discovery rate (FDR) to reduce Type I error due to the large number of genes analyzed simultaneously. Statistical significance is set at $p \leq 0.05$. Findings will be correlated with clinical and demographic variables. *Mechanistic interactions between transcript expression and functional pathway enrichment analysis* of differentially expressed genes will be performed using ClusterProfiler v3.14.3 packaged within the R environment v3.6.3 in Gene Ontology (GO) biological processes, molecular function, and cellular component, and disease ontology terms.

Aim 2. We will test the hypothesis FC display greater alterations in classes of genes related to the spliceosome, cell death, cell signaling and tau pathology in DSD+ vs DSD- and PreC using long-read RNA sequencing. Long-read RNA sequencing will extend the limited splicing and tau related information obtained from our Nanostring data. This technique will reduce any ambiguity associated with analysis and detection of transcripts. Due to budget limitations, RNAseq will be done in the FC and PreC in DS, but not in AD. This aim will be performed for Dr. Jensen at TGen using the traditional ***Illumina and Long-Read Oxford Nanopore Technology (ONT)***. Targets differentially expressed, unique to one group of cells, or associated with disease will be prioritized in the ONT data analysis. We will verify ONT splice changes in the higher depth Illumina sequencing for further prioritization of potential targets. Standard analyses such as differential expression, clustering, PCS, heatmaps, and pathway analysis will be performed to describe the data in detail. RNA splicing changes will be validated using RNAScope technique that provides subcellular localization and confirmation of splice changes.

Proposed One-Year and Long-Term Outcomes:

Each aim was designed for a duration of a year and since all the techniques are used routinely in our research, we do not expect any delays (COVID-willing). DS and AD FC and PreC tissues are already in-house so will start when moneys are recieved. The studies proposed here will provide funds to respond to our NIH R01 grant criticism.

Year End Progress Summary:

While the end goal of this project was to perform ***single population expression profiling combined with custom-designed microarray analysis*** in double U1-70K+AT8 and U1-70K+TauC3 positive neurons, and single non-tangle-bearing nuclear U1-70K neurons using Laser-capture-microdissection, and RNA sequencing in frozen using the traditional ***Illumina and Long-Read Oxford Nanopore Technology (ONT)*** in a year, due to the COVID-19 pandemic, brain tissue samples from DS subjects, both fixed and frozen, arrived later than expected from the Brain Bank, delaying the beginning of our experiments. So, tissue staining for the LCM, and the long-read RNA sequencing is on-going and at the present the results are not finalized for these experiments.

By contrast, the Illumina short-read RNA sequencing has been performed and currently data is being analyzed by Dr. Kendall van Keuren-Jensen at TGen. Part of the Illumina RNA sequencing findings were added as preliminary and feasibility data to our recently submitted NIH R01 grant entitled “Default mode network dysfunction in Down Syndrome” on June 3rd, 2022.

Figure 5 shows the differential expression of genes in the FC between demented and non-demented DS subjects using the traditional RNA sequencing Illumina in collaboration with TGen. This data was added to the grant. Figure 6 illustrates some of the genes differentially expressed in the FC between demented and non-demented DS subjects. Once our data is completed, findings will be published in a peer-reviewed journal, and we expect to obtain more intriguing preliminary findings for a new grant submission. Our proposal, expects to lay the foundation for a wide range of targets for potential interventions via transcriptionally aided drug design to treat dementia in DS with translation to AD.

Our expenses included immunohistochemistry materials, LCM reagents, and RNA sequencing materials and salaries. We are grateful to the AAC for supporting our DS research, which findings will be presented and disseminated in the medical/research community. It has also ensured an opportunity for us to become leaders in the research of DS.

In fact, as a representation of our flourishing DS research, recently, in collaboration with Phoenix Children’s Hospital, we published two manuscripts showing deficits in neuronal differentiation in the hippocampus and frontal cortex, brain structures involved in cognitive functions, in early postnatal stages of development in Down syndrome in the Journal of Clinical Medicine and Acta Neuropathologica Communications, respectively.

- 1) Moreno DG, Utgawa EC, Arva NC, Schafernak KT, Mufson EJ, Perez SE. Postnatal Cytoarchitecture and Neurochemical Hippocampal Dysfunction in Down Syndrome. J Clin Med. 2021 Jul 31;10(15):3414. doi: 10.3390/jcm10153414. PMID: 34362198; PMCID: PMC8347520.
- 2) Utgawa EC, Moreno DG, Schafernak KT, Arva NC, Malek-Ahmadi MH, Mufson EJ, Perez SE. Neurogenesis and neuronal differentiation in the postnatal frontal cortex in Down syndrome. Acta Neuropathol Commun. 2022 Jun 8;10(1):86. doi: 10.1186/s40478-022-01385-w. PMID: 35676735; PMCID: PMC9175369.

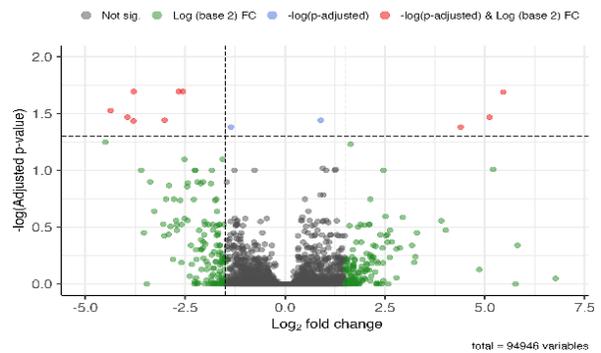


Figure 5. Volcano plot of differentially expressed FC genes between DSD+ (n=10) and DSD- (n=6) cases. Red dots indicate genes with Bonferroni adjusted $p < 0.05$ and $> 1.5X$ fold change; green $> 1.5X$ fold change only, and blue adj. $p < 0.05$ only. Grey dots are not significant.

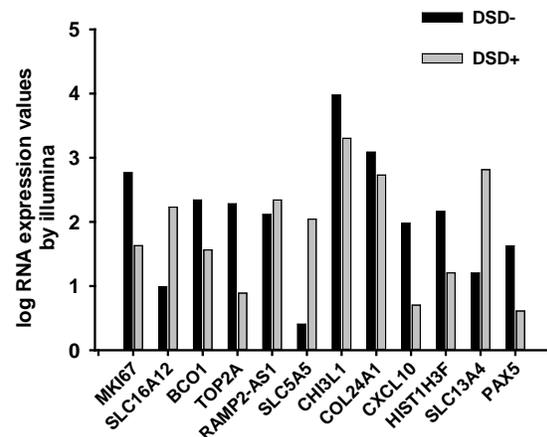


Figure 6. FC Illumina data showing differential gene expression of several transcription (TOP2A and PAX5) and inflammation related proteins (CHI3L1, CXCL10) between DSD- and DSD+. All genes showing here were significantly upregulated or downregulated between groups ($p < 0.05$).

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Role of TDP-43 proteinopathies in AD and related dementias. Rita Sattler, PhD, Elliott Mufson, PhD, Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Specific Aims:

Specific Aim 1: Identify and compare neuronal gene expression alterations caused by nuclear TDP-43 depletion versus cytoplasmic accumulation in postmortem fusiform gyrus tissue from AD, MCI, and NCI subjects.

Specific Aim 2: In vitro validation of candidate genes for their role in TDP-43 pathology using mammalian cell lines and patient iPSC cortical neurons.

Background and Significance:

Cytoplasmic aggregations of TDP-43 were initially identified in postmortem tissue of FTD and ALS patients^{2,3}. However, cytoplasmic inclusions of TDP-43 are also found in 19-57% of AD cases^{4,5}. TDP-43's cellular functions include transcription, splicing, miRNA biogenesis, mRNA transport, stability and translation^{6,7}. There is a concerted effort to elucidate mechanisms by which TDP-43 leads to neurodegeneration, to understand pathways leading to wild-type TDP-43 accumulation, and the contribution of TDP-43 protein/RNA complexes to the disease process. Most molecular pathobiologic studies have focused on the role of TDP-43 in ALS and FTD, with little examination in other dementias. By contrast, most investigations of TDP-43 inclusions in AD are clinical pathological studies describing a staging system of TDP-43 pathology^{1,8}. However, it was reported that the volume of the fusiform gyrus (Brodmann area 37), a region in the inferior temporal cortex that plays important roles in object and facial recognition, was reduced in TDP-43 positive tissues compared to TDP-43 negative cases in AD¹. Overall, our understanding of the molecular pathobiology of TDP-43 inclusions in the fusiform cortex is greatly under investigated.

Preliminary Data, Experimental Design and Methods:

We had obtained preliminary data confirming the presence of TDP-43 cytoplasmic inclusions in the medial temporal gyrus of AD patient tissue obtained from the Banner Sun Health brain and body donation program (Drs. Beach and Serrano). We further showed that we have the ability to isolate neuronal nuclei depleted of TDP-43 from AD patient tissue using fluorescent activate cell sorting (FACS) technology.

Our experimental approach was aimed at using FACS to isolate TDP-43-depleted neuronal nuclei from patient tissues of NCI, MCI and AD patients, perform RNA sequencing analyses and compare the transcriptomic data to those obtained from TDP-43 containing nuclei.

In addition, we proposed to use laser capture microscopy (LCM) to isolated whole neurons with cytoplasmic TDP-43 inclusions, followed by RNA isolation and RNA sequencing. We aimed to compare the transcriptomic data from isolated TDP-43-depleted nuclei to those from whole neurons (nuclei and cytoplasm) with TDP-43-positive cytoplasmic inclusions.

Finally, after bioinformatics analyses and candidate gene ranking of differentially expressed genes (DEGs) in both of these experimental groups, we proposed to validate these candidate gene in AD-TDP-43 positive patient derived iPSC cortical neurons.

Proposed One-Year and Long-Term Outcomes:

We posit for the first time neuronal transcriptomic aberrations in TDP-43-depleted neuronal nuclei and neurons with cytoplasmic inclusions in AD compared to MCI, a prodromal stage of AD. Data generated will be integrated into a NIH proposal to study transcriptional mechanisms underlying TDP-43 pathology during the progression of AD.

Year End Progress Summary:

Specific Aim 1: Identify and compare neuronal gene expression alterations caused by nuclear TDP-43 depletion versus cytoplasmic accumulation in postmortem fusiform gyrus tissue from AD, MCI, and NCI subjects.

Gene expression changes of neurons with TDP-43-depleted nuclei

To isolate RNA from TDP-43-depleted nuclei for transcriptomic analyses, we proposed fluorescent activated cell sorting (FACS) from AD/MCI/NCI patient postmortem autopsy tissue (fusiform gyrus) previously confirmed for TDP-43 mislocalization by immunohistochemistry. To establish and validate this protocol, TDP-43 positive postmortem tissue from ALS patients (frontal cortex) was used. Optimization steps included tissue homogenization, nuclei isolation and staining of nuclei with fluorescent markers for nuclear protein NeuN and for TDP-43. The use of two fluorescent markers allowed us to separate NeuN-positive nuclei with TDP-43 (supposed healthy neurons) and NeuN-positive nuclei without TDP-43 (supposed diseased neurons), confirmed via fluorescent microscopy of isolated nuclei after FACS.

Once TDP-43+/- nuclei were separated, RNA was immediately isolated and processed for RNA sequencing (at TGen in collaboration with Dr. Van Keuren-Jensen) and for quantitative PCR (qPCR) of select marker genes.

The results of these optimization steps confirmed transcriptional changes between the diseased and healthy neurons. Ongoing studies are now transferring this protocol to AD-TDP-43+ postmortem fusiform gyrus tissue samples obtained from the Banner Sun Health Brain and Body donation program (Drs. Beach and Serrano). The data from these ongoing studies will be included in a R01 submission scheduled for December 2022.

Gene expression changes of neurons with TDP-43 cytoplasmic aggregations

Tissue sections from the same patients will also be processed for laser capture microscopy (LCM). This will allow us to not only capture nuclear RNA, but also cytoplasmic RNA in those neurons characterized with TDP-43 pathology. To establish and validate this protocol, we again used existing TDP-43 positive ALS patient postmortem tissue sections (motor cortex). To obtain sufficient quality RNA from laser captured neurons, the handling of the brain tissue during the necessary immunostaining steps (labeling for neuronal marker and for TDP-43) should not exceed one hour. This requirement necessitated careful optimization steps regarding the fixation of the tissue and the testing of numerous antibody sources that would allow for the maintenance of RNA integrity after the LCM at the same time as the importance of the proper identification of TDP-43 positive/negative neurons.

The result of this optimization is now allowing us to perform LCM on the designated AD/MCI/NCI postmortem tissue samples. Isolated RNA will be sequenced at TGen and the data will be included in the above noted R01 submission in December.

Challenges encountered

The optimization of these methods for our specific project has turned out to be more challenging than expected and hence took much longer. In addition, we encountered technical problems with the FACS equipment at BNI and are now switching over to using the FACS equipment at TGen instead, which again led to additional validation and optimization experiments.

Specific Aim 2: In vitro validation of candidate genes for their role in TDP-43 pathology using mammalian cell lines and patient iPSC cortical neurons.

Induction of TDP-43 pathology in mammalian cell lines

To establish a culture model system with cytoplasmic TDP-43 mislocalization (and nuclear depletion), we used the mammalian neuron-like cell line SH-SY5Y. We obtained endogenously-

tagged TDP-43-EGFP SH-SY5Y cells from Dr. Don Cleveland's laboratory at UCSD. Using this line, we established protocols to mislocalize TDP-43 by addition either Sodium Arsenite or Sorbitol, two stressors that had been shown previously to induced TDP-43 mislocalization. Mislocalization is monitored by immunostaining and the quantification of the nucleocytoplasmic ratio of TDP-43, as we have shown in previous publications and for other RNA binding proteins. We were able to quantify this mislocalization and to reduce the extend of mislocalization using proprietary small molecule compounds proposed to bind to TDP-43 RNA binding domains. Furthermore, we established a biochemical readout by performing cellular fractionation of cells with and without stressors and comparing the levels of TDP-43 in the nucleus versus the cytoplasm.

Patient iPSC cortical neurons of AD-TDP-43+ patient subgroup

While with significant delay, we finally obtained the newly reprogrammed AD-TDP-43+ iPSCs. These iPSC are currently expanded and are in the process of being differentiated into iPSC cortical neurons using established protocols in the laboratory. These iPSC cortical neurons will be analyzed for TDP-43 pathology and function as described in the original proposal.

Challenges encountered

The significant delay in receiving our reprogrammed iPSC clones did not allow us to obtain any data from patient-derived cells. We are catching up with these experiments as we speak and will have sufficient preliminary data for the December R01 submission.

Future grant applications, publications and collaborations that arose from the research.

A NIH/NIA R01 will be submitted in December using the preliminary data generated from this award. Our collaborative efforts with Dr. Mufson and his team, as well as Dr. Van Keuren-Jensen and her team will enable us to submit a strong R01 application.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Finger Tapping Abnormalities and Reduced Functional Upper-Extremity Movement as Predictors of Cognitive Decline in Older Adults with Memory Complaints. George P. Prigatano, PhD, Ashley M. Stokes, PhD, Sydney Schaefer, PhD, Anna Burke, MD. Barrow Neurological Institute; Arizona State University; Arizona Alzheimer's Consortium.

Specific Aims:

Aim 1: Demonstrate that motor deficits (finger tapping abnormalities and reduced functional upper-extremity movement) can predict cognitive decline in older persons with memory complaints. We hypothesize that baseline performance on both measures will be associated with conversion from amnesic mild cognitive impairment (MCI-A) to Alzheimer's Disease (AD) over a 1-year follow-up. We also predict that persons with Subjective Memory Complaints (SMC) without objective memory impairment will perform normally on both finger-tapping and functional upper-extremity tasks and will not convert to AD over a 1-year follow-up.

Aim 2: Investigate neuroimaging and neuropsychological correlates of these two motor tasks to ascertain the functional domains susceptible to early neurodegeneration. We hypothesize that the functional domains activated by these two motor-based assessments will include frontal-parietal connectivity reductions indicative of executive functional decline. We anticipate that neuropsychological measures of executive dysfunction will correlate with motor findings in the MCI and AD samples.

Background and Significance:

Cognitive decline is a common concern in aging populations. A proportion of older individuals exhibit a mild but objective decline in their memory (MCI), and these patients have a higher risk of progressing to AD. In addition, individuals who complain of memory impairment but demonstrate normal performance on tests of memory may be classified with SMC. Identifying individuals with SMC and MCI on either trajectory (to develop or not develop AD) is important for reducing emotional distress and helping them and their families make decisions concerning their future care. Recent research has pointed out that subtle fine motor tasks, which are less emotionally threatening to older adults, may have both prognostic and diagnostic value when evaluating patients suspected of developing a dementing condition such as AD. For example, finger tapping measures (speed, inter-tap intervals, and variability) have shown differences between healthy older individuals and those with AD and MCI. Additionally, other upper-extremity tasks may be a better predictor of functional decline in MCI than standardized cognitive measures.

Unfortunately, large-scale clinical studies using neuropsychological measures to assess AD phenotypes and risk profiles have largely overlooked the value of fine motor performance. To address this limitation, this study will investigate whether motor task abnormalities may have diagnostic value for separating SMC patients from AD and MCI and for identifying which MCI patients will progress to AD. Combining these metrics with an advanced MRI protocol will provide insight into the underlying early neuropathological changes associated with altered motor task performance.

Preliminary Data:

Preliminary findings from our ongoing research study revealed normal finger tapping performance in older healthy control (HC) participants and persons with subjective memory complaints (SMC) with no objective evidence of memory impairment. In contrast (and as predicted), patients with documented MCI-A demonstrated slower and more variable tapping speeds. Interestingly, these patients also exhibited greater difficulties inhibiting adjacent finger

movements when performing the task and have a higher rate of “invalid” tapping movements while performing our modified finger-tapping test. In line with our initial hypotheses, MCI patients demonstrate subtle but clinically relevant difficulties when performing a finger tapping task that involves *initiating and sustaining* speed of index finger movement while simultaneously *inhibiting* other adjacent finger movements. Additionally, the Motor Rehabilitation and Learning Lab (directed by Dr. Sydney Schaefer, Co-I) has shown that their self-administered motor task is a predictive of decline in MCI in both subjective and objective measures of daily functioning. More recent pilot data has shown MCI patients who convert to AD had smaller practice effects than those who were stable, even though the two groups had similar memory scores. This is consistent with the premise that reduced practice effects on neuropsychological assessments may be a prognostic index for disease progression.

The second aim of this study is to investigate neuroimaging correlates using an advanced MRI protocol that will be indicative of network changes associated with the observed motor performance changes. We (Stokes, Co-PI) previously developed an advanced MRI protocol specifically for use in aging and Alzheimer’s populations, which specifically probes functional activation and connectivity across cognitive domains. As part of our prior studies, we found voxel-wise correlations between motor task performance and imaging biomarkers, as well as group differences in white matter integrity.

Experimental Designs and Methods:

This study is a longitudinal group design with repeated measures, comprised of four groups of participants, including normally functioning older adults, SMC, MCI, and probable early AD. A standard clinical neuropsychological examination will be conducted for all patient groups. This clinical evaluation will include a clinical interview, the BNI Screen for Higher Cerebral Functions (BNIS), Wechsler Adult Intelligence Scale-IV, Rey Auditory Verbal Learning Test, Brief Visual Memory Test-R, Trail Making Test A and B, and the modified version of the Halstead Finger Tapping Test. Prior to MRI, participants will also perform a self-administered motor task. MRI will be performed at 3T (Philips). The MRI protocol will include structural imaging (to assess atrophy patterns), microstructural imaging (using diffusion MRI to assess WM changes), perfusion MRI (to assess blood flow), and functional MRI with both resting-state and task-based paradigms (to assess connectivity and functional activation patterns). We will assess motor task measures across groups, as well as neuroimaging correlates of these metrics.

Proposed One-Year and Long-Term Outcomes:

The prior year of funding has laid the foundation for this longitudinal expansion study by establishing a baseline set of neuropsychological and imaging phenotypes across the HC, SMC, MCI-A, and AD cohorts. Our results show promise for motor biomarkers to separate these cohorts, and we anticipate publication of these results using cross-sectional design. The longitudinal follow-up enabled by the current proposal will enable identification of stable non-converters and converters. These results will identify predictive biomarkers using motor tasks (including a self-administered task that may further enable early screening) and neuroimaging biomarkers. The data obtained through this funding will be used for a larger grant application through the National Institute on Aging. **We ultimately envision an expanded understanding of the cognitive and functional domains associated with motor changes and a greater appreciation of the potential role of motor-based biomarkers in AD risk.**

Year End Progress Summary:

Four subject groups were recruited for this study, including healthy control (HC), SMC, MCI, and AD. Neuropsychological data was collected for all subjects, while a subset of the cohort also underwent MRI scanning. The mean age was similar across cohorts (mean age \pm standard deviation: 73.5 \pm 6.7, 68.2 \pm 4.7, 75.3 \pm 5.6, and 73.8 \pm 4.8 for HC, SMC, MCI, and AD,

respectively). The majority of subjects were right-handed. Educational attainment (in years) across cohorts was 15.3, 16.3, 15, and 14.8 for HC, SMC, MCI, and AD cohorts, respectively.

Baseline and follow-up neuropsychological data was entered into a REDCap database for each participant and assessment. Preliminary analysis shows a trend for the BNIS across cohorts, where the HC, SMC, MCI, and AD groups show age-corrected total T-scores of 53.8 (SD 8.7), 54.3 (SD 6.2), 27.0 (SD 9.9), and 20.0 (SD 6.8), respectively. Domain-specific trends in the BNIS were observed for memory and visuospatial sub-scores, with more subtle trends in awareness, orientation, and language. For the HFTT scores, we observed mean finger-tapping scores of 41, 42, 42, and 37 (right hand) and 37, 37, 36, and 33 (left hand) across the HC, SMC, MCI, and AD groups, respectively. The range of scores was 10, 10, 13, and 16 for the right hand and 8, 8, 12, 18 for the left hand across the HC, SMC, MCI, and AD groups, respectively. Finally, the number of invalid taps was 0.5, 0.2, 1.3, and 3.2 (right hand) and 1.4, 0.7, 3.3, and 4.5 (left hand) across the groups. In all cases, the left hand shows a higher rate of invalid taps than the right hand, as expected. Interestingly, we find a high level of invalid tapping lateralization in the MCI group, but in the AD group there is more bilateral representation. We hypothesize that in the early stages of AD-associated neurodegeneration, the ability to sustain valid tapping movements is lateralized due to differential regional neurodegeneration; as the effects of neurodegeneration increasingly impact more regions of the brain in the later AD stages, this laterality effect reduces and yields more bilateral invalid tapping rates. *This is the first time such an observation has been made and demonstrates the novel information provided by finger-tapping motor assessments.* These findings are further bolstered by our self-administered motor task, which showed trends for intrasubject deviation (ISD) for the non-dominant hand. More specifically, the dominant ISD was 4.8, 7.6, 5.6, and 3.3 for the HC, SMC, MCI, and AD groups, respectively, while the non-dominant ISD was 4.9, 15.3, 10.0, and 9.8 for the HC, SMC, MCI, and AD groups, respectively. Further analysis of scores for the remaining cognitive assessments is currently underway across groups.

For the MRI data, segmentation and parcellation was performed on the structural T_1 -weighted images using standard FreeSurfer (<http://www.freesurfer.net>) pipelines. Diffusion MRI data underwent our standard pipeline, including denoising, distortions, motion and eddy current correction, bias field correction, and brain extraction. Standard diffusion tensor imaging (DTI) parameters were obtained using *dtifit* (FSL, <https://fsl.fmrib.ox.ac.uk/fsl/>). An in-house Matlab script was used to correct the DTI metrics for free-water (isotropic motion) components, and anatomically-constrained tractography is underway to assess structural connectivity. Functional MRI analysis steps include motion alignment, distortion correction, de-spiking, and temporal alignment. Subsequently, dynamic maps of quantitative relaxation times are generated to assess global and microvascular activation. All images are then normalized to standard space and group-wise statistical analysis of task response is performed for each task. For resting-state fMRI, independent component analysis (ICA) is performed to assess functional connectivity. Correlations between neuropsychological assessments and neuroimaging data were performed using Spearman's correlations. Preliminary analysis of free-water corrected fractional anisotropy (FA, reflective of white matter integrity) showed reduced FA in the MCI group relative to the SMC and HC groups, as well as lower FA to a smaller extent in SMC compared to HC (FDR<0.05, Bonferroni corrected). The white matter tracts showing these trends include the anterior thalamic radiation (bilateral), superior longitudinal fasciculus (left), corpus callosum, and anterior corona radiata (left). In contrast, the free-water component (reflective of neurodegeneration) showed higher free-water in MCI relative to SMC and HC, and slightly higher free-water in SMC relative to HC. The associated regions included the cingulum, corpus callosum, and fornix. Additionally, FA was inversely correlated with non-dominant ISD in a cluster covering parts of the internal capsule, anterior corona radiata and thalamic radiation, and the superior fronto-occipital fasciculus. Further data analysis for MRI is ongoing.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Hispanic Enrollment in Alzheimer's Research Trials (The H.E.A.R.T. Program at BNI). Yonas E. Geda, MD, Anna D. Burke, MD, Krista Hanson PhD, Marwan Sabbagh, MD. Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, St. Joseph's Westgate Medical Center, Chandler Regional Medical Center, Mercy Gilbert Medical Center; Arizona Alzheimer's Consortium.

Specific Aims:

1. Implementation of the HEART Program includes a formal development plan outlining internal and external outreach strategies to increase recruitment and the establishment of organizational infrastructure, resources, and written translational materials to promote trial retention while recognizing 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 Promotors 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 100 participants, 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. The enrollment goal for BNI will be to have 40-50 actively enrolled Hispanic participants by 2023.

Proposed One-Year and Long-Term Outcomes:

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 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 screens. To support the core in recruiting, enrolling, and retaining 100 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. The enrollment goal for BNI will be to have at least 50-60 actively enrolled Hispanic participants by 2023.

An outline of BNI's specific aims to achieve the above-stated enrollment and retention goals includes:

1. Recruitment of 25 new Hispanic enrollees in the next year.
2. Retention of 100 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 grow the number of bilingual staff members within our program 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 Yonas Geda, MD/Meredith Wicklund, 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. We quadrupled the number of Spanish speaking staff members over the past year, including the addition of a new psychometrist who is not only fluent in both Spanish and English but also has a significant amount of experience administering cognitive tests/questionnaires that are specific to the geriatric population we serve. The addition of these Spanish speaking staff members has significantly enhanced our ability to reach community members, retain existing participants and gather more accurate data.
2. BNI staff worked relentlessly to maintain our existing relationships with Hispanic study participants while also enhancing the site's ability to communicate meaningfully with the Hispanic community. Over the past year we have begun preparing three of our bilingual staff members to take the Spanish medical translation certification exam. One of these staff members is our research psychometrist who administers the cognitive assessments; these are a crucial part of gathering the data necessary to improve our understanding of how AD specifically affects the Hispanic members of our AD community. The impact of giving a patient the opportunity to communicate comfortably in their chosen language cannot be overstated and in this specific area BNI has made great progress over the past year.
3. We partnered with Univision to develop an informative segment titled "***Conoce los síntomas del Alzheimer, enfermedad mental que aumenta entre la comunidad hispana***" (*Know the symptoms of Alzheimer's, an illness of the mind that is increasing among the Hispanic community*). This segment consisted of a televised interview with one of our most experienced study coordinators, Angelica Garcia, and was conducted entirely

in Spanish. Univision is a well-known news source in the Hispanic community with a broad, multinational audience. The segment remains available on the Univision Arizona website for viewers who may not have caught the initial airing.

4. We continued conducting regular Spanish speaking “Memory Cafes” for individuals with AD and their loved ones to find support, education and resources on AD. This group was the first and only of its kind when it began and remains a highly praised asset within the community.
5. Our partnership with the Promotores program remains strong as they are able to expand our reach to the community by fostering collaboration among organizations with similar goals for the Hispanic population.
6. We have finalized the production of the dementia tip cards that have been translated into Spanish and contain helpful information for patients and caregivers on how to deal with common situations that are often more challenging to navigate in the presence of Alzheimer’s disease (e.g. bathing/hygiene, driving). The dementia tip cards are regularly distributed to our Hispanic patients and their loved ones who consistently provide positive feedback regarding their usefulness.
7. We have continued to translate the consent forms for our actively enrolling trials. Since our last update, we have been able to pay for translational services on three trials for which an accurate ICF is essential to our ability to responsibly enroll study participants whose primary or preferred language is Spanish.
8. We have been able to expand access to educational activities for BNI staff that provide insight into the problem of Alzheimer’s disease and the specific impacts it has on the Hispanic community. This year we sent two study coordinators to the 3rd Annual Latinos and Alzheimer’s Symposium in early 2022.
9. We completed production of the Spanish version of the dementia caregiving guide and other culturally sensitive outreach materials that had just finished development at the end of last year. These have been invaluable resources for many of our Hispanic participants and their care partners.
10. Over the past year, we enrolled a total of 7 Hispanic participants, with an overall total of 28 active Hispanic participants. Although the ongoing COVID-19 pandemic did limit our ability to conduct in-person outreach activities to the degree we would have liked, it did not limit BNI’s motivation to work toward the stated goals of the program. Despite limitations the BNI staff did continue to organize and participate in outreach activities across the Valley when feasible. As we look ahead to what lies in store for next year there is no doubt that the diligent and consistent efforts put forth by BNI staff who strive to improve the lives of our Hispanic patients and community members will be invaluable. Our dedication to enhancing not only the number of Hispanic patients interacted with but, perhaps more importantly, the quality of those interactions will prove crucial in our goal of establishing deep community ties.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Complement C3aR deficiency alleviate VCID progression. Saif Ahmad, PhD. Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Dignity Health; Arizona Alzheimer's Consortium.

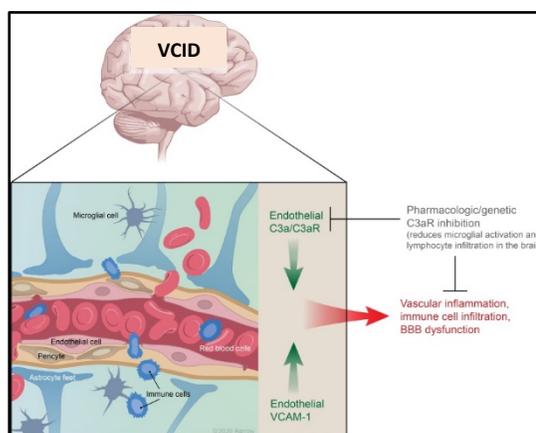
Specific Aims:

Cognitive impairment and dementia causes great economic and social burden and is projected to affect 75.6 million people worldwide by 2030 [1]. Vascular contributions to cognitive impairment and dementia (VCID) comprise 50% of the cases of dementia. VCID encompasses the entire clinical spectrum from mild cognitive impairment to full-blown dementia and there remains no effective treatment available for VCID [1-3]. Therefore, our **long-term goal** is to understand the molecular mechanism of VCID to facilitate development of therapeutics to prevent the progression of vascular-related dementia.

White matter damage (WMD) remains the pathological hallmark of VCID and is often visualized in the periventricular regions and centrum semiovale. The imaging correlate of this WM damage is "leukoaraiosis" [4]. The degree and severity of leukoaraiosis are associated with cognitive impairment, depression, gait abnormalities, and disability [4]. Reduction in cerebral blood flow (CBF) leading to hypoperfusion is an early and characteristic finding. Several reports suggest neuroinflammation plays a crucial role in WM injury and cognitive dysfunction induced by chronic cerebral hypoperfusion. **Complement activation, especially component C3 and C3aR, plays a significant role in the progression of ischemic brain injury, Alzheimers disease and age-related cognitive decline** [5, 6]. Complement component C3 potentiates age-related and neurodegenerative changes in the CNS via its C3a anaphylatoxin which, in conjunction with its cognate receptor C3aR on the endothelial cells exacerbates vascular injury in the brain [6, 7].

C3aR-mediated endothelial VCAM-1 expression has been shown to promote chronic vascular injury associated with aging [77]. Although activation of the C3a/C3aR pathway is "**inevitable**" even with healthy aging, understanding the signaling mechanism that contribute to the vascular injury and decline in cognitive function remains unexplored. Our studies will utilize the widely accepted mouse bilateral carotid artery stenosis (BCAS) model that reproduces the WM damage, cerebral hypoperfusion, inflammation, BBB damage, and cognitive deficits seen in humans [8, 9]. Our **preliminary data** shows that C3aR expression is significantly increased in the brain endothelium, hippocampus and frontal cortex following BCAS, and that C3aR knockout mice have increased cerebral perfusion and improved cognitive function following BCAS relative to wild-type mice. We **hypothesize that increased endothelial C3a/C3aR signaling will exacerbate vascular injury, WMD and impair cognitive function following BCAS. We propose the following specific aims:**

SPECIFIC AIM 1: Test the hypothesis that C3aR deficiency regulates endothelial VCAM1 signaling in VCID. We will utilize the C3aR^{-/-} mice to demonstrate the functional and



Scheme 1. C3aR-mediated endothelial cell VCAM1 expression increases in the cortex and hippocampus, disrupts tight junctions, which increases BBB permeability. RBCs, plasma proteins, and leukocytes can infiltrate the vasculature where into extravascular tissue.

pathophysiological role of C3aR expression in the resident-tissue vs. circulating cells. Mice subjected to BCAS will be followed for at least 4-wks to test them on a battery of behavioral tests, imaging for WMD and CBF, tissue biochemistry and histopathological studies in the brain. Blood will be also collected for FACS-analysis of immune responses.

SPECIFIC AIM 2: Test the hypothesis that C3aR deficiency protects BBB integrity and prevents VCID progression. For this Aim, we will utilize endothelial *C3ar1* knockout (T2KO) mice. Mice will be subjected to BCAS injury and followed for behavioral, imaging, biochemical and histopathological outcomes as above in Aim 1.

Expected outcomes: We anticipate that the genetic deletion of endothelial *C3aR* will reduce cerebral hypoperfusion, WM damage, inflammation, BBB damage, and cognitive deficits. **Impact:** Our mechanistically-driven therapeutic approach which will identify a novel role for endothelial C3aR in cognitive deficits has far reaching **translational implication** in VCID. With this pilot funding, our goal is to generate sufficient preliminary data from Aims to apply for R21/R01 grant on VCID, a recognized research priority at the NIH.

Background and Significance:

A. SIGNIFICANCE: Over the past several decades, the majority of cognitive decline has been attributed to AD. This view has evolved with the understanding that Vascular Dementia (VaD) comprises up to 20% cases of dementia, while vascular causes contribute in more than 50% of cases [3, 10, 11]. Therefore, the NINDS Stroke Progress Review Group in 2012 cited “the prevention of **VCID** (**V**ascular **C**ontributions to **C**ognitive **I**mpairment and **D**ementia)” as a major research priority, which encompasses the development of mild to severe cognitive decline. Importantly, age is the most important unmodifiable risk factor for VCID. The risk for VCID rises with age, doubling every ~5.3 years [11, 12], implicating a greater public concern. However, to this date no effective treatment is available. Thus, our study will provide the insight into molecular mechanism of VCID to facilitate translation of therapeutics to prevent the progression of dementia.

A1. Dynamics of Cerebral circulation in VCID

During the process of aging, the cerebral vasculature and other components of the NVU undergo multiple changes that predispose the brain to neurovascular diseases, including VCID. Reduction of cerebral blood flow (CBF) is key precipitating event in VCID due to the brain’s superior sensitivity to alterations in CBF [13-16]. Hypoperfusion is an early finding that plays a pathophysiological role in the development of white matter (WM) damage [3, 17, 18]. A penumbra exists around white matter lesions that expand in relation to lower blood flow [19-21]. Hypoperfusion usually precedes cognitive dysfunction and cause neurodegeneration deeper into the WM [10, 17, 19, 20, 22-26]. However, the signaling molecules involved in the variability of cerebral blood flow to progression of VCID are unknown. Our studies will address this important gap by use of a physiologically relevant BCAS model in mice to gather critical data for understanding the signaling that lead to progression of VCID.

A2. Should we target Endothelial Cells in blood vessels?

WM changes are mediated by vascular dysfunction, inflammation, and blood-brain barrier (BBB) leakage [22, 27-29]. The leading structural feature of cerebral vessels is the formation of a blood-brain barrier (BBB). The BBB is composed of tight junctions (TJ) and adherens junctions between endothelial cells, as well as other cellular components, such as the basal membrane, pericytes, and astrocyte endfeet [30, 31]. Loss of vessel integrity is thought to drive BBB dysfunction, and can be found in numerous neurological disease conditions, namely traumatic brain injury, stroke, and neurodegeneration [32]. Multiple studies have reported increased BBB permeability in

dementia, which contributes to neurodegeneration and functional decline [33-37]. However, how the increase in BBB permeability leads to progression of VCID is unknown. Furthermore, evidence shows that vascular inflammation, marked by increased endothelial expression of vascular cell adhesion molecule VCAM1, stokes CNS aging [38, 39]. Although elevated levels of VCAM1 to correlate with Parkinson's disease severity [40] and, recently, lymphocytes known to bind VCAM1 in brain vasculature were found in aged and AD patient brains [41, 42]; the contribution of endothelial VCAM 1 in WM changes and functional decline is unknown.

A3. Does Complement play a role in VCID?

The complement cascade is an integral part of innate immunity [43, 44]. The active signaling peptide of C3, C3a, is released via cleavage by the extracellular enzyme C3 convertase and acts in conjunction with its cognate receptor to complement immunity [6, 45, 46]. Aberrant release of C3a is detrimental and promotes vascular injury [47, 48]. We and others have shown that elevated plasma levels of C3a in conjunction with the increased expression of its receptor C3aR exacerbate acute brain injury and chronic neurodegeneration in animal models of stroke, TBI and VCI [7, 48-54]. Although C3a generation occurs in both healthy aging and neurodegenerative disorders, a comprehensive pre-clinical understanding of C3a/C3aR molecular signaling in VCID progression is still lacking. This study will provide foundation for future preclinical assessment of C3aRA therapy for prevention of VCID that has **never** been accomplished.

Preliminary Data, Experimental Design and Methods:

Our novel data now shows that C3aR expression is significantly increased in the "**brain endothelium**". Greater circulatory C3a and cerebral C3aR expression in VCID vs. WT/KO mice. We observed Hippocampal and Corpus Callosum injury in C57/B6 male mice. Sagittal sections of hippocampus show shrinkage above the CA1 region in BCAS compared with Sham and KO-VCI mouse. Significant degeneration of Corpus Callosum was also observed in BCAS relative to sham and KO-VCI (C3aR^{-/-}) mice. WT-VCID animals showed decrease cerebral perfusion compared with Sham and KO-VCI (C3aR^{-/-}) mouse as observed by Laser Speckle and MRI data. WT-VCID animals showed increased VCAM-1 expression and cognitive deficits compared with Sham and KO-VCI (C3aR^{-/-}) mouse in both NORI and Morris Water Maze spatial reference memory task. Interestingly WT-VCID animals showed increased ventricle volume compared with Sham and KO-VCI (C3aR^{-/-}) mouse as observed with MRI.

Proposed One-Year and Long-Term Outcomes:

We expect that long-term follow up after BCAS will confirm the development of VCID and resultant dementia, as determined by our behavioral test. Surviving mice will demonstrate poor muscular strength and coordination, loss of gait control, neuropsychiatric dysfunction (increased depression and anxiety) and impairment in learning-memory, at 4-wks post-injury. Moreover, BCAS- mice will demonstrate a loss of cerebral microvascular density, increased neuroinflammation, and demyelination (WM damage). We anticipate that genetic C3aR deletion will improve microvascular plasticity and reparative angiogenesis to reduce neuroinflammation and protect WM integrity. Given our past experience, we do not anticipate significant mortality (<5%) with BCAS- models.

For Aim 2: We expect greater endothelial C3aR and VCAM1 expression in BCAS mice, loss of tight junction proteins and recruit inflammatory lymphocytes infiltration in WM and tissue injury. We also anticipate C3aR deficiency will improve cognitive functions in BCAS mice.

Year End Progress Summary:

We have successfully completed this ARC funded project. In AIM 1, we proposed that C3aR deficiency regulates VCAM1 signaling and alleviate progression of VCID in BCAS mouse model.

We found that VCAM expression was high in brain hippocampus in C57Bl/6-VCID mice and C3aR deletion attenuates VCAM1 expression level. We observed that C3aR deficiency improved cerebral blood flow, white matter degeneration and brain inflammation compared with WT-VCID mice. In our second AIM, we found that C3aR deficiency significantly improved BBB integrity and cognitive functions. Overall, C3aR deficiency showed interesting results and these data led us to create endothelial C3aR KO mice to explore further the role of C3aR in vascular dementia and work is in progress. Based on our findings we were able to submit NIH R21 grant with our collaborator Dr. Jennifer Sullivan (Professor, Augusta University) and Dr. Kanchan Bhatia from ASU. Our findings from this funded grant have been published in the reputable journal *Translational Stroke Research*.

- Bhatia K, Kindelin A, Nadeem M, Khan MB, Yin J, Fuentes A, Miller K, Turner GH, Preul MC, Ahmad AS, Mufson EJ, Waters MF, Ahmad S, Ducruet AF. Complement C3a Receptor (C3aR) Mediates Vascular Dysfunction, Hippocampal Pathology, and Cognitive Impairment in a Mouse Model of VCID. *Transl Stroke Res*. 2022 Oct;13(5):816-829. doi: 10.1007/s12975-022-00993-x. Epub 2022 Mar 8. PMID: 35258803.

**MAYO CLINIC ARIZONA
PROJECT PROGRESS REPORTS**

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Normal and Pathological Aging (Preclinical Alzheimer's Disease). 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 3000 participants from which were selected our study population for further testing. We have completed one or more epochs of neuropsychological testing on 903 individuals including 500 APOE e4 noncarriers, 280 e4 heterozygotes, and 110 e4 homozygotes (APOE results pending in 14) with followup durations of up to 28 years (average is nearly 10 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).

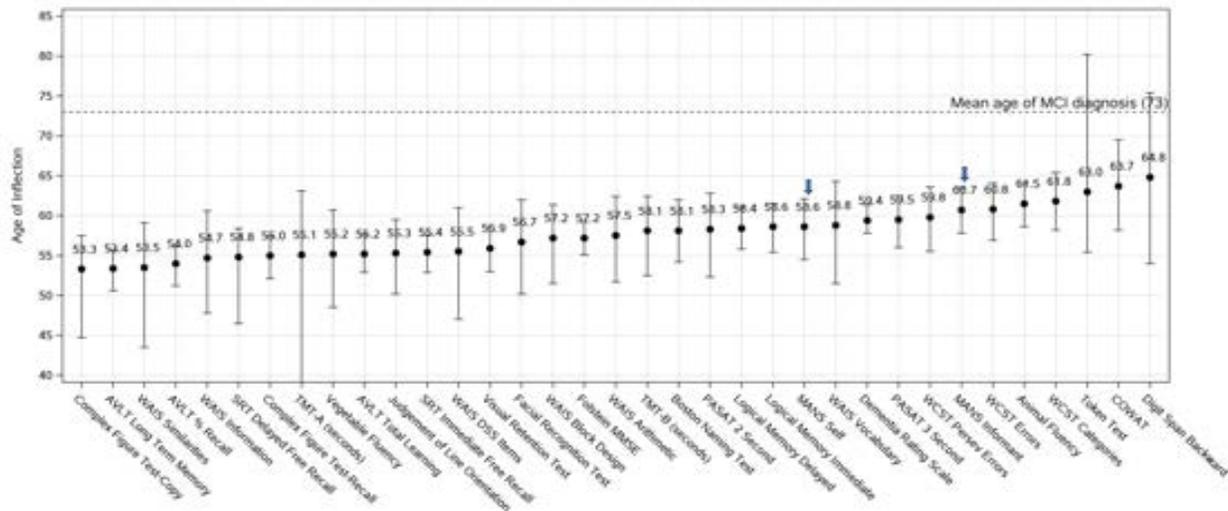
Proposed One-Year and Long-Term Outcomes:

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 continued failure (and relative inefficacies) of amyloid targeted clinical trials (8).
3. We are providing collaborative support to multiple investigators at Arizona State University (Yalin Wang, David Brafman, Michael Sierks, William Tyler, 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).

References:

1. Caselli RJ, Dueck AC, Osborne D, Sabbagh MN, Connor DJ, Ahern GL, Baxter LC, Rapcsak SZ, Shi J, Woodruff BK, Locke DE, Snyder CH, Alexander GE, Rademakers R, Reiman EM. Longitudinal modeling of age-related memory decline and the APOE epsilon4 effect. *N Engl J Med.* 2009 Jul 16; 361 (3):255-63
2. Caselli RJ, Dueck AC, Locke DE, Hoffman-Snyder CR, Woodruff BK, Rapcsak SZ, Reiman EM. Longitudinal modeling of frontal cognition in APOE epsilon4 homozygotes, heterozygotes, and noncarriers. *Neurology.* 2011 Apr 19; 76 (16):1383-8
3. Caselli RJ, Locke DE, Dueck AC, Knopman DS, Woodruff BK, Hoffman-Snyder C, Rademakers R, Fleisher AS, Reiman EM. The neuropsychology of normal aging and preclinical Alzheimer's disease. *Alzheimers Dement.* 2014 Jan; 10 (1):84-92
4. Caselli RJ, Dueck AC, Locke DE, Sabbagh MN, Ahern GL, Rapcsak SZ, Baxter LC, Yaari R, Woodruff BK, Hoffman-Snyder C, Rademakers R, Findley S, Reiman EM. Cerebrovascular risk factors and preclinical memory decline in healthy APOE epsilon4 homozygotes. *Neurology.* 2011 Mar 22; 76 (12):1078-84
5. Caselli RJ, Dueck AC, Locke DE, Henslin BR, Johnson TA, Woodruff BK, Hoffman-Snyder C, Geda YE. Impact of Personality on Cognitive Aging: A Prospective Cohort Study. *J Int Neuropsychol Soc.* 2016 Aug; 22 (7):765-76 Epub 2016 June 27
6. Caselli RJ, Langlais BT, Dueck AC, Henslin BR, Johnson TA, Woodruff BK, Hoffman-Snyder C, Locke DEC. Personality Changes During the Transition from Cognitive Health to Mild Cognitive Impairment. *J Am Geriatr Soc.* 2018 Apr; 66 (4):671-678
7. Caselli RJ, Langlais BT, Dueck AC, Chen Y, Su Y, Locke DEC, Woodruff BK, Reiman EM. Neuropsychological decline up to 20 years before incident mild cognitive impairment. *Alzheimers Dement.* 2020 Mar; 16 (3):512-523.
8. Caselli RJ, Knopman DS, Bu G. An agnostic reevaluation of the amyloid cascade hypothesis of Alzheimer's disease pathogenesis: The role of APP homeostasis. *Alzheimers Dement.* 2020 Nov; 16 (11):1582-1590

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Nanobody development for Alzheimer's disease targets. John D. Fryer, PhD. Mayo Clinic Arizona; Arizona Alzheimer's Consortium

Project Description:

APOE and CLU are among the most prominent Alzheimer's disease risk genes. A recent preclinical study in an Alzheimer's disease mouse model demonstrated that an anti-APOE monoclonal antibody was able to reduce amyloid load. Our own published data indicated that CLU is a strong therapeutic target, and may even act in concert with APOE. In this proposal we aim to develop and characterize several potential therapeutic single-chain antibodies derived from llamas ("nanobodies") directed against APOE or CLU.

Specific Aims:

Specific Aim 1. Use our clone pools from our already screened phage display library to find anti-APOE and anti-CLU nanobody clones.

Specific Aim 2. Assess whether anti-APOE or anti-CLU nanobody clones are suitable as research reagents (Western, immunostaining, immunoprecipitation).

Specific Aim 3. Test the ability of nanobody clones to reduce levels of APOE or CLU in vivo.

Background and Significance:

Human genetic studies across tens of thousands of individuals have identified several genetic variants that alter the risk for developing Alzheimer's disease. Aside from the APOE and TREM2 genes, the majority of these new Alzheimer's genes are linked to noncoding genomic variants and are thought to influence expression of these genes either at baseline or in the context of disease course (or both). Additionally, only a handful of these genes have been pursued with rigorous functional studies in vivo to determine what role they play in disease pathogenesis. The clusterin (CLU) gene, aka apoJ, is one such Alzheimer's risk gene that, like APOE, functions as a lipoprotein and has roles in amyloid metabolism and regulating inflammation. Our lab has been at the forefront of CLU studies and we have demonstrated that CLU influences the amount and location of amyloid deposition (Wojtas et al., 2020b, 2017), and more recently that CLU impacts tau pathology (Wojtas et al., 2020a). APOE has long been a proposed therapeutic target for Alzheimer's disease given its roles in modulating both amyloid and tau pathology, and a recent study found that a monoclonal antibody against APOE was able to reduce amyloid pathology in a mouse model (Xiong et al., 2021). This immunotherapy approach has not been attempted for CLU. In this proposal, we will characterize and validate several novel, unique single-chain antibodies derived from llamas ("nanobodies") against both APOE and CLU. Nanobodies are encoded by a single nucleotide sequence that gives rise to a single peptide chain of only about 15kDa in size compared to conventional monoclonal antibodies that are derived from heavy and light chains and are ~150kDa. Their small size makes them more blood-brain barrier penetrant, and their single nucleotide nature makes them easily amenable to cloning and molecular display technologies like phage display that allow screening for antigenic targets rapidly. Nanobody clones can also be inexpensively produced in massive quantities using bacterial expression systems. We have recently generated a naïve nanobody library cloned from a large, diverse pool of white blood cells derived from 20 different llamas. Naïve nanobody libraries are increasingly popular as they save a significant amount of time and cost, and this approach was used to successfully and rapidly generate a blocking nanobody against SARS-CoV-2 that is in clinical trials. Two rounds of positive selection of this nanobody phage library revealed several potential binders against human APOE and human CLU. We have used ELISA to screen the first of several clones for each and identified N=7 unique nanobodies for APOE and N=4 unique nanobodies for

CLU at the time of proposal submission. We have performed Sanger sequencing and found that the overall nanobody structure is intact and that these clones are unique. Additionally, the APOE nanobodies do not bind to CLU, and the CLU nanobodies do not bind to APOE.

Preliminary Data:

As described above, we have already screened our diverse nanobody library and selected dozens of potential binders to both APOE and CLU. Our initial characterization found that, as expected, a few of these clones for each were redundant. Sequencing analysis also found a few clones that lacked normal nanobody structural domains and we did not pursue these. We have not yet tested our initial nanobody clones for their ability to work for Western blotting, immunostaining, or immunoprecipitation, but those are the next steps. For this molecular characterization, we will be capitalizing on our absolutely unique humanized CLU mouse line that we recently generated from an NIH-funded R03 grant. This knock-in mouse has the endogenous murine CLU gene replaced with the human CLU gene from the start codon to the stop codon, with all exonic/intronic sequences intact. It additionally contains loxP sites for conditional knockout studies. This is identical in concept to the humanized “targeted replacement” APOE2, 3, or 4 mice that are used widely in the Alzheimer’s disease field. We have verified that these mice express human CLU in the proper spatiotemporal pattern as murine CLU. We have bred to the APP/PS1 amyloid mouse model and found that amyloid plaque formation is slightly delayed, but the pathology is otherwise mostly normal. We have also gone a step further and crossed our hCLU mice onto APOE3/3 or APOE4/4 mice, and these double homozygous mice will serve as a tool to test for the molecular assays proposed.

Proposed One-Year and Long-Term Outcomes:

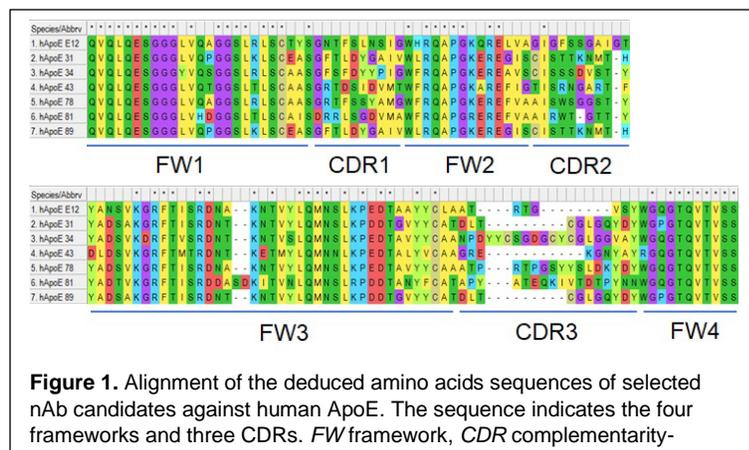
For the next year, we will:

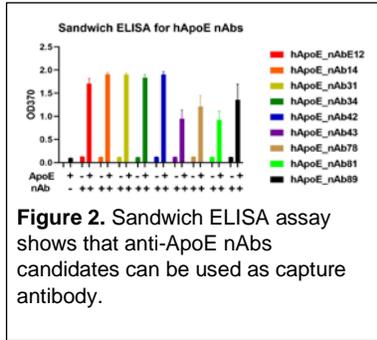
1. Continue to screen additional nanobodies from immunized libraries
2. Test binding affinities through solid phase assays
3. Test the best binders on their ability to be used as molecular reagents (immunoprecipitation, western blotting, immunostaining, ELISA)
4. Test the optimal binders for the ability to reduce APOE or CLU levels in vivo
5. Test the best nanobodies for their ability to reduce amyloid load, tau pathology, or associated neuroinflammation

Year End Progress Summary:

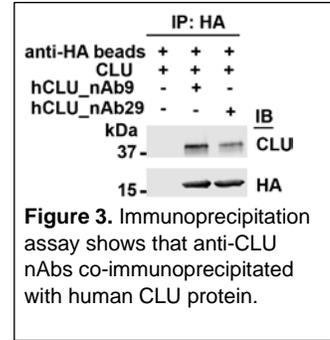
We have completed screening of our diverse nanobody (nAb) library and selected dozens of potential binders to both APOE and CLU. We have performed Sanger sequencing and found that the overall nAb structure is intact and that most clones are unique, as expected, and that a few of

these clones were redundant (**Figure 1**). Sanger sequencing analysis also found a few clones that lacked normal nAb structural domains and we did not pursue these. We have purified initial nAbs against APOE and CLU. The yields of these nAbs are in the range of 1-10 mg from 1 L of bacterial culture. We also have confirmed their application in sandwich enzyme-linked immunosorbent assay (ELISA) as the capture antibody to recognize the human ApoE protein



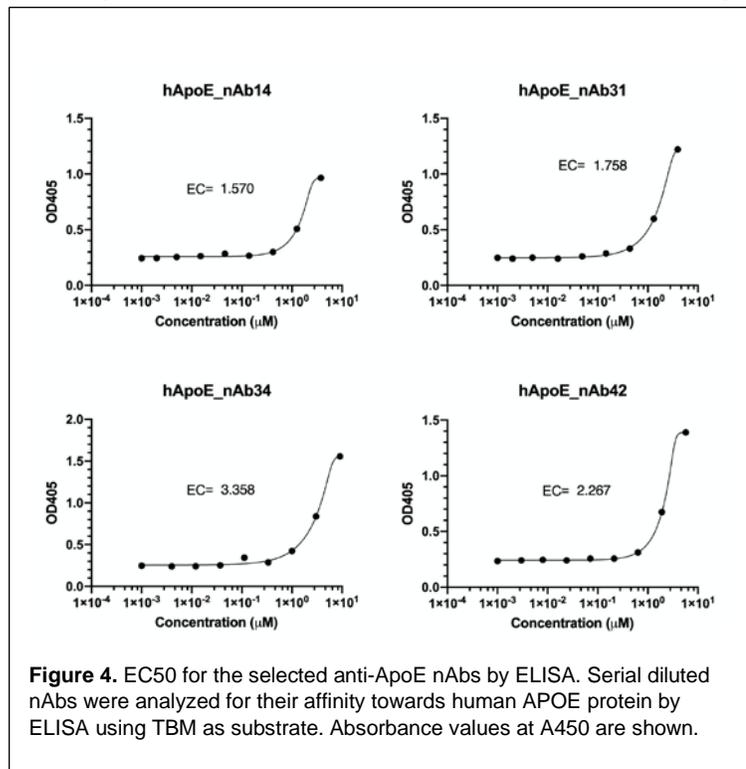


(**Figure 2**). Furthermore, we found that our anti-CLU nAbs were successfully able to immunoprecipitate human CLU protein from normal human serum (**Figure 3**). We also have estimated the apparent affinity for nAbs (EC50) by ELISA (**Figure 4**), though we will pursue more refined methods for true affinity characteristics. Nevertheless, we estimate the EC50 for these anti-APOE nAbs are in the micromolar



range. While these affinities are reasonable, we decided to generate a target enriched library by immunization of a llama with APOE and CLU proteins. We have received the blood from these immunized llamas, cloned the nAb into phagemids, and have performed 2 rounds of phage display to identify several more unique binders that have a much higher likelihood of displaying high affinity binding.

In summary, we have successfully identified several nAb candidates for ApoE and CLU. Characterization of their therapeutic function *in vivo* will be our immediate study as we plan to pursue purified nAb injections into WT and amyloid mice as well as clone into AAV vectors for proof-of-concept “gene therapy” approaches.



**MIDWESTERN UNIVERSITY
PROJECT PROGRESS REPORTS**

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 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. Midwestern University; Arizona Alzheimer's Consortium.

Specific Aims:

Senescence Accelerated Mouse-Prone 8 (SAMP8) mice is a sub-strain of senescence-accelerated mice (SAM) and characterized by an early manifestation of age-related phenotypes, including age-related deficits in learning and memory (1, 2). We propose to use SAMP8 mice to test intermittent fasting as an intervention that systemically affects the rate of aging, thereby mitigating the risk of Alzheimer's Disease (AD).

- *Specific Aim 1: To define the effects of intermittent fasting on cellular senescence in peripheral tissues of aged SAMP8 mice*

Specific Aim 1 will test our hypothesis that intermittent fasting will decrease tissue accumulation of senescent cells. The levels of senescence markers in the tissues of SAMP8 mice on *ad libitum* control and intermittent fasting (i.e., every-other-day feeding) will be analyzed by various methods.

- *Specific Aim 2: To explore the effect of intermittent fasting on age-related changes in the brain of SAMP8 mice*

In Specific Aim 2, we hypothesize that intermittent fasting alleviates age-related pathological changes in the brain of SAMP8 mice. The following will be analyzed: (i) oxidative damage and mitochondrial dysfunction, (ii) the levels of amyloid precursor protein (APP), phosphorylated tau, and presenilin, and (iii) the cognitive function.

Background and Significance:

The number of Americans aged 65 and older was 46.2 million in 2014, representing 14.5% of the U.S. population or one in every seven Americans. By 2060, there will be an estimated 98 million older persons, which is more than twice their number in 2014. Since aging is a critical risk factor in a variety of human pathologies including AD, determining the causal cellular and molecular processes that lead to functional decline and frailty is crucial for achieving a goal of "healthy aging". The evidence increasingly supports the connection between cellular senescence and organismal aging (3).

Recently, intermittent fasting has emerged as a more palatable alternative to caloric restriction (4). Many studies have shown that intermittent fasting can have similar effects as caloric restriction (5). In humans, intermittent fasting has been shown to improve numerous health conditions. Similarly, intermittent fasting also has been shown to have beneficial effects in rodents. Although intermittent fasting has been suggested to have numerous anti-aging effects, the mechanisms underlying the beneficial effects of intermittent fasting are understudied. Especially, the impact of intermittent fasting on cellular senescence has been rarely studied.

We hypothesize that the beneficial effects of intermittent fasting result from the suppression of cellular senescence in peripheral tissues. Given the strong association between aging and AD,

we further hypothesize that suppression of cellular senescence in peripheral tissues will decrease the incidence and progression of AD. Our hypotheses will be tested using the SAMP8 mice.

Preliminary Data, Experimental Design and Methods:

Thirty-two SAMP8 mice were used in this study (2 groups: *ad libitum* vs. intermittent fasting, 8 males and 8 females/group). SAMP8 mice for the experiment were generated from our breeding colony established at MWU. The animals were provided *ad libitum* access to water and a standard laboratory diet until 2 months of age. Two-month-old SAMP8 mice were randomly assigned to two groups. The *ad libitum* group continued to receive food *ad libitum*, whereas the intermittent fasting group was fed *ad libitum* every other day (EOD) for 9 months. At the termination of the experiment, 11-month-old mice were sacrificed, and various tissues were harvested. The tissues were processed for subsequent analysis of senescence markers and AD pathology.

Proposed One-Year and Long-Term Outcomes:

To our knowledge, this is one of the few studies that investigate the long-term effects of intermittent fasting on aging using a mouse model of early aging. This study will determine the effect of intermittent fasting on the levels of senescence as well as the development of AD-like pathology in a mouse model of early aging. This study resulted in the development of collaborative studies with Drs. Layla Al-Nakkash and Seungyong Lee (Department of Physiology, College of Graduate Studies, Midwestern University). Three medical students are currently working on this project as their summer research program. The findings from this study will be presented in Kenneth A. Suarez Research Day at MWU as well as in the 2022 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 aim 1

We found that SAMP8 mice under intermittent fasting for 9 months were lean while the mice under regular feeding protocol (*ad libitum*) were obese. Moreover, we found that intermittent fasting improved glucose control in aged SAMP8 mice while *ad libitum* group exhibited an impaired glucose tolerance, a sign of insulin resistance. Furthermore, the molecular analysis identified that intermittent fasting significantly reduced the levels of senescence markers in the fat tissue of the aged SAMP8 mice. In addition, age-related fat accumulation in the liver and pancreatic beta-cell hyperplasia were significantly reduced in aged SAMP8 mice subjected to intermittent fasting. Analysis of other tissues for senescence is currently in progress.

- Specific aim 2

In this funding period, we established Barn's maze and Morris water maze (MWM) tests. Although they are widely used to study spatial memory and learning and are considered to be one of the "gold standards" of behavioral neuroscience, the system for these tests was not previously available in the Glendale campus. Using the tests that we established, we found that intermittent fasting significantly improved memory function in aged SAMP8 mice. We are currently analyzing the effect of intermittent fasting on AD-like pathology in the brains of the aged SAMP8 mice.

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 that investigate 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.

Recently, the National Institute of Aging (NIA) released multiple new funding opportunities seeking applications for the understanding of **(i)** how age-associated metabolic changes, including insulin resistance, in the brain and peripheral tissues affect the onset and/or progression of AD and **(ii)** how aging/senescence of the brain and peripheral systems impact the development and progression of AD [(a) <https://grants.nih.gov/grants/guide/notice-files/NOT-AG-21-053.html> (release date: 01-07-22), (b) <https://grants.nih.gov/grants/guide/notice-files/NOT-AG-21-039.html> (release date: 12-03-2021), and (c) <https://grants.nih.gov/grants/guide/notice-files/NOT-AG-21-041.html> (release date: 01-06-2022)]. The areas of research in these Notices of Special Interest from NIA highly overlap with the research goals of our project in this proposal (i.e., insulin resistance and cellular senescence).

References

1. Takeda T, Matsushita T, Kurozumi M, Takemura K, Higuchi K, Hosokawa M. Pathobiology of the senescence-accelerated mouse (SAM). *Exp Gerontol.* 1997;32(1-2):117-27. Epub 1997/01/01. PubMed PMID: 9088909.
2. Takeda T. Senescence-accelerated mouse (SAM): a biogerontological resource in aging research. *Neurobiol Aging.* 1999;20(2):105-10. Epub 1999/10/28. PubMed PMID: 10537019.
3. Bhatia-Dey N, Kanherkar RR, Stair SE, Makarev EO, Csoka AB. Cellular Senescence as the Causal Nexus of Aging. *Frontiers in genetics.* 2016;7:13. Epub 2016/02/24. doi: 10.3389/fgene.2016.00013. PubMed PMID: 26904101; PMCID: 4751276.
4. de Cabo R, Mattson MP. Effects of Intermittent Fasting on Health, Aging, and Disease. *N Engl J Med.* 2019;381(26):2541-51. doi: 10.1056/NEJMra1905136. PubMed PMID: 31881139.
5. Shetty AK, Kodali M, Upadhy R, Madhu LN. Emerging Anti-Aging Strategies - Scientific Basis and Efficacy. *Aging Dis.* 2018;9(6):1165-84. doi: 10.14336/AD.2018.1026. PubMed PMID: 30574426; PMCID: PMC6284760.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Exploring intestinal microbiota dysbiosis in transgenic Alzheimer's disease mouse models. Garilyn Jentarra, PhD, T. Bucky Jones, PhD, Fernando Gonzalez, PhD, Doug Jones, PhD, Johana Vallejo, PhD, Vanthida Huang, PharmD, and Pam Potter, PhD. Midwestern University; Arizona Alzheimer's Consortium.

Specific Aims:

Based on preliminary data showing dramatic differences in the gut microbiota of APOE versus 3xTg mouse models of AD, we *hypothesize* that the presence of AD-associated transgenes in mouse models will alter their gut microbiomes even if the animals are co-housed with each other. We will test this hypothesis using the following specific aims:

- 3) Evaluate differences in composition of intestinal microbiota in APOE3, APOE4, and 3xTg mice versus C57BL/6 control mice at 6-weeks, 4-months, and 6-months of age.
 - a. We will perform 16 rRNA gene sequencing on fecal pellets from mice. Returned data will be analyzed for differences in bacterial microbiota between the control housed mice and the different strains of hetero-housed mice.
 - b. Material from fecal pellets will be cultured for the presence of common fungi, including *Candida* and *Aspergillus* among others [1], to evaluate potential differences between mouse strains.
- 4) Evaluate how the presence of AD-associated transgenes influences the microbial population and integrity of the intestinal tracts in APOE3, APOE4, and 3xTg mice versus C57BL/6 control mice.
 - a. We will solubilize mouse fecal pellets and analyze for the presence and quantity of secreted amyloid- β .
 - b. We will perform immunohistochemical analysis of mouse small and large intestine for amyloid- β and for indicators of increased intestinal permeability.

Background and Significance:

Dysbiosis of the gut microbiota has been repeatedly implicated in the development of AD [2]. Proposed mechanisms have included inflammatory processes, increased permeability of the intestinal and blood-brain barriers, seeding and propagation of amyloid- β [3], translocation of gram-negative bacterial components to the brain [4], bacterial production and metabolism of neurotransmitters and tryptophan [5]. Some studies have directly assessed differences in the gut microbiota of AD patients in comparison to cognitively normal controls. A 2017 study found that AD patients had a decreased abundance of Firmicutes and an increased abundance in Bacteroidetes, as well as a significantly decreased *Bifidobacterium*, a common gut microbe normally found at high levels in the human gut. That study also correlated those changes with an increase in cerebrospinal fluid biomarkers of AD, suggesting a link between the dysbiosis and the development of abnormalities consistent with AD [6]. A 2018 study identified six bacterial taxa that were significantly altered in AD patients in comparison to normal controls [7]. A variety of studies have also proposed using antibiotics or probiotics in AD patients to alter the gut microbiota with the intention of decreasing inflammation and intestinal permeability [8, 9]. A small study found that treatment with probiotics (*Lactobacillus species* and *Bifidobacterium bifidum*) substantially improved mini-mental state examination (MMSE) scores in just 12 weeks. Also improved in that study were markers of insulin metabolism (which is impaired in AD along with glucose metabolism), and triglyceride levels. Decreases in C-reactive protein (CRP) and malondialdehyde (MDA), were observed, indicating decreased inflammatory processes [10]. Our group and others [11] have also identified bacterial DNA sequences in the brain tissue of AD patients, suggesting

that bacteria may translocate from the gut, and potentially other body sites, to the brain and it is possible that a loss of the integrity of the intestinal barrier might exacerbate this.

Other researchers have also found, as we inadvertently did, that alterations of gut microbiota can be seen in various mouse models of AD. A recent study using the 5xFAD and 3xTg mouse models found dysbiosis in both models, worsening with age. Housing of young 3xTg mice with older 3xTg mice accelerated brain pathology, potentially via transfer of microbiota. [12] A study using 3xTg mice found changes in the most prominent bacterial taxa as well as metabolic alterations that were magnified by age or high fat diets [13]. A 2018 study in APP/PS1 mice measured changes over time and found that while bacterial populations in the gut were similar at 3 months, they had diverged significantly by 6 months, a time point at which amyloid pathology becomes apparent in both this strain [14] and the 3xTg model [15].

Preliminary Data, Experimental Design and Methods:

We previously performed 16SrRNA gene sequencing on fecal pellets from mice. We noted a *striking* difference in the gut microbiomes of APOE transgenic mice versus 3xTg mice and it is this difference that we would like to continue to explore in the current grant proposal.

In APOE transgenic mice, Lactobacillus and Muribaculaceae accounted for ~75% of the reads in each sample. In 3xTg mice, the microbiota was dominated primarily by Lachnospiraceae_NK4A136 and Lachnospiraceae, with smaller amounts of Turicibacter and Roseburia. Lactobacillus and Muribaculaceae were nearly absent from the 3xTg mice, which is particularly notable since they normally make up a large part of the intestinal microbiota of mice. Lactobacilli are well known to be beneficial residents of the gut of most mammals, including humans, and Muribaculaceae and Lachnospiraceae, are known to metabolize mucus-derived monosaccharides, which can protect against colonization by pathogenic microbes such as *C. difficile* by competing for this resource [16]. The previously mentioned study in APP/PS1 mice also noted an unusual amount of Turicibacter [14], similar to what we observed in the 3xTg mice. This microbe is noticeably absent in APOE mice.

The mice in this study were produced and raised in colonies housed in the MWU animal facility. All housing, food, and water were from the same source. Their backgrounds are similar, C57BL/6 for the APOE mice and likely C57BL/6-129S4 for the 3xTg mice (the original derivation of this model is a little unclear and C57BL/6 is often used as the control line). Given these similar environmental and genetic backgrounds (except for the presence of the transgenes), we did not expect such dramatic differences in the gut microbiota of the APOE versus 3xTg mice.

We will be using mice of four strains in the proposed experiments. Wild type mice (C57BL/6) will serve as controls for the APOE strains as well as the 3xTg model. 3xTg mice for the experiments will be produced in our existing colony. APOE3 and APOE4 mice will be purchased in addition to the C57BL/6 mice. All mice will be separated into the planned housing scheme:

Control mouse cages: For each mouse strain, 3 male mice will be housed together, and, in a separate cage, 3 female mice of that strain will be housed together. In total, 6 mice of each strain will serve as controls for fecal microbiota for the strain.

Hetero-housed mice: Mice will always be housed only with mice of the same sex. In each cage there will be one mouse of each strain, hence 4 mice per cage.

Aim 1.1: DNA extractions will be performed on fecal pellets using the Qiagen DNeasy PowerSoil kit. DNA will then be sent to TGen for 16S rRNA gene sequencing. TGen will also provide standard data analysis. Data will be analyzed collectively per strain and using age and sex as variables. We will also specifically evaluate whether the microbiota of the hetero-housed mice deviates from their strain controls. This will provide information about whether the transgenes may inhibit the adoption of another strain's typical microbiota.

Aim 1.2: Additional fecal pellets will be homogenized and evaluated for the presence of common fungi using appropriate fungal growth plates. Relative patterns of fungal growth will be assessed by strain, sex, and age.

Aim 2.1: Fecal pellets will be solubilized, and the resulting solution analyzed for the presence and quantity of amyloid- β via ELISA. Statistical analysis in SPSS software will be performed to assess differences by age, sex and strain.

Aim 2.2: Mice will be sacrificed at 6 months of age. Fecal pellets, intestine, blood, and brain tissue will be collected (blood and brain may be used in subsequent follow up experiments). We will perform immunohistochemical analysis on tissue sections of the small and large intestine to analyze for intracellular amyloid in epithelial cells as well as increased intestinal permeability as visualized by a decrease in zonula occludens-1, which is a scaffolding protein for tight junction proteins.

Proposed One-Year and Long-Term Outcomes:

One-Year Outcomes: In combination with our previous data, we anticipate that this work will form the basis of a publication as well as provide the preliminary data needed for grant proposals. The NIH has earmarked funding specifically for proposal searching for a link between microbes in the body and the development of AD. The Infectious Diseases Society of America has also been offering funding devoted to proposals focused on this topic. We believe that if we can provide strong preliminary data, we will be competitive for funding from either of these sources.

Long-Term Outcomes: The experiments proposed here are intended to validate and extend our previous work. We hope this work will add to the body of knowledge applicable to AD and lead to better understanding of the mechanisms by which the disease occurs. If our hypothesis proves correct, we will explore whether the presence of specific taxa in the gut lead to increased permeability of the intestinal barrier and correlates with increased amyloid plaque formation.

Year End Progress Summary:

This study is still underway. We have currently collected samples at two of the three time points. DNA has been extracted from fecal pellet samples from the two collected timepoints and prepared for sequencing analysis. Once all timepoints are collected, the DNA will be sent as a set for 16S rRNA sequencing to determine the relative abundance of bacterial taxa. Data analysis will include comparisons by age, sex, and mouse strain. Additional pellets are being stored for analysis of fungal organisms and for quantitation of amyloid beta secreted in the gut. These tests will be conducted when all samples have been collected.

After the final time point for fecal pellet collection, mice will be sacrificed and intestine, blood, and brain tissue will be collected. Blood and brain tissue will be stored for future analysis. Intestine will be used for histochemical analysis to evaluate measures of intestinal permeability, for comparison between strains, sexes, and ages.

Issues encountered: The study started later than anticipated due to breeding issues in the 3xTg colony. Once those issues were resolved, we attempted to order in age-matched APOE3 and APOE4 mice but found that the APOE3 mice were unavailable and would be for some time. We proceeded with the experiments using just the APOE4 mice. As previous experiments in APOE3 and APOE4 mice had found their gut microbiomes to be very similar, we decided that the WT C57BL/6 mice would be used as the only control strain.

We will have the data from most of the experiments by early fall 2022 and will promptly analyze all data. We will subsequently (1) draft a manuscript with the findings (in combination with previous relevant data) and (2) use the data to write an NIH R15 or R21 funding application and prepare an application for the IDSA's Microbial Pathogenesis in Alzheimer's Disease Grant, which will open in January 2023.

ARIZONA ALZHEIMER'S CONSORTIUM
2021-2022 Scientific Progress Report

A genome-wide screen for human proteins that affect amyloid beta peptide production by gamma secretase using a yeast genetic system. Mark J. Swanson, PhD, Nancy S. Bae, PhD. Midwestern University; Arizona Alzheimer's Consortium.

Specific Aim:

Identify human cDNAs that affect the total activity of γ -secretase in a reconstituted yeast system.

Background and Significance:

Alzheimer's disease (AD) is an age-related disease characterized the accumulation of amyloid beta (A β) peptides into plaques that inhibit proper brain function and lead to neurodegeneration. The molecular mechanism of A β production and regulation is poorly understood. However, mutations in the genes coding for amyloid precursor protein (APP) and the presenilins (PS1 and PS2) are frequently seen in familial forms of AD. APP is a transmembrane protein first cleaved by the β -secretase enzyme to produce a membrane-bound fragment called C99. This fragment is further cleaved by γ -secretase to produce peptides of variable lengths, predominantly the soluble A β 40 and to a lesser extent A β 42, which tends to aggregate forming plaques. γ -secretase is a multi-subunit protein complex with either presenilin1 or 2 proteins (PS1 or PS2, encoded by the *PSEN1* and *PSEN2* genes, respectively). Three additional proteins are required for enzymatic activity, Anterior Pharynx-1 (Aph-1), Nicastrin (Nic) and presenilin enhancer 2 (Pen2).

Human γ -secretase activity was previously reconstituted in the yeast *Saccharomyces cerevisiae*. In this system, all four subunits of the γ -secretase complex were expressed from high-copy yeast plasmids using strong promoters. The target they used to measure the activity of the complex contained a portion of the APP protein made up of 55 amino acids of the 99 amino acid carboxy-terminal fragment, which contains the γ -secretase cleavage site. This was fused to the yeast GAL4 transcriptional activator protein. The normal *GAL4* gene was deleted from the chromosome. The bacterial *lacZ* gene, encoding beta-galactosidase, was used as a reporter by placing GAL4 binding sites near the promoter of the gene. Thus, beta-galactosidase activity was used as a proxy for γ -secretase activity. When the C55-GAL4 fusion protein is expressed in yeast, the C55 portion is embedded in the plasma membrane, trapping the GAL4 protein at the cellular periphery, preventing it from activating reporter genes in the nucleus. Only when γ -secretase is active, and the C55 portion is cleaved, will GAL4 be released from the membrane and enter the nucleus where it can bind DNA and activate nearby genes. Other labs use this system to study the γ -secretase subunits and mutations with in them. There are currently no studies that investigate protein modulators of γ -secretase. *In our research, we aim to identify novel protein modulators of γ -secretase activity that may be useful in identifying new AD susceptibility loci, AD resistance genes, and targets of therapeutic, as well as to provide insight into the mechanisms for producing amyloid peptides leading to plaque formation, a hallmark of AD pathology.*

Preliminary Data:

In our lab, we have successfully reconstituted γ -secretase activity in yeast by designing a system suited to our needs. We have cloned the four subunits of γ -secretase that are required for activity. We have chosen to use PS1 as the catalytic subunit instead of PS2 as the majority mutations leading to eFAD are in the *PSEN1* gene. The γ -secretase subunits are expressed from plasmids. Our target gene for γ -secretase activity is a fusion of C99, the natural target of γ -secretase, and the yeast GAL4 transcriptional activator. C99-GAL4, is expressed from the chromosome to avoid issues of plasmid number variability. We replaced the naturally occurring yeast *MET17* gene locus with the *C99-GAL4* fusion gene. To allow us to use *MET17* as a

selectable marker for a plasmid. We modified two yeast strains for use in our system, each with several reporter genes under GAL4 control. Activity of γ -secretase is measured by determining the expression of the reporter genes. For some of these reporter genes, only cells having active γ -secretase can survive. In one of the strains, we have a counter-selectable marker so only cells with no γ -secretase activity can survive.

Our goal is to use our system to identify novel proteins that can act as modulators of γ -secretase activity. Towards this end, we tested two proteins we are studying in the laboratory that form a ternary complex with PS1. GFAP ϵ is an isoform of the glial fibrillary acidic protein with an unknown function that was identified as interacting with the amino terminus of PS1. The RAP1 protein is a telomere-associated factor that has also non-telomeric roles. Our lab identified GFAP ϵ as an interacting partner of RAP1. Additional work indicated that all three proteins can interact to form a complex. When we tested their effects on γ -secretase activity, we observed that when RAP1 and GFAP ϵ were simultaneously expressed, total γ -secretase activity increased four-fold.

Experimental Design and Methods:

Using the yeast γ -secretase system designed in our lab, we will identify novel protein modulators of human γ -secretase activity. We would like to identify both positive and negative regulators of γ -secretase. Our current system yields activity that is too strong to use in a screen based on growth selection to identify modulators that increase activity. However, we would be able to identify proteins that decrease activity using the counter-selectable marker mentioned above. To screen for activators of γ -secretase activity, we need to reduce the activity of γ -secretase in our current system. Currently we are using high-copy plasmids to express the subunits of γ -secretase. We will change these to single copy plasmids. As a backup plan to this, we can replace the strong yeast promoters driving the expression of the γ -secretase subunits by weaker promoters.

Using this system, we will screen cDNA libraries made from RNAs isolated from human neuronal cell lines, specifically SH-SY5Y neuroblastoma and U251 glioblastoma cells, both of which are widely used in the AD field. We are choosing neuronal cell lines since our interest is in the production of A β peptides in the brain. Since a change in A β peptide production may be due to oxidative stress, and we have studied oxidative stress in the lab, we would like to grow the neuronal cell lines under normal and oxidative stress conditions as a way to increase the chances we may isolate both negative and positive modulators of γ -secretase.

RNA will be purified from these cells and converted into copy DNA (cDNA). The cDNAs will be cloned into a vector we have planned for this experiment. The plasmid will have the yeast *MET17* selectable marker. It will be a high-copy plasmid in yeast with a strong promoter driving the expression of the cDNA that we will fuse to a start codon and an epitope tag for detection using antibodies. The use of a high-copy plasmid and a strong promoter will allow us to express more of the cDNA than the γ -secretase subunits ensuring we will see an effect. We will use an *E. coli* vector with the kanamycin resistance gene as a selectable marker. The plasmids expressing the γ -secretase subunits all have the ampicillin resistance marker, so the use of the kanamycin marker will allow us to quickly and easily purify plasmids that modulate γ -secretase activity. Once we isolate colonies that show a modulation of γ -secretase, we will screen them for additional activities to ensure that the effects are not due solely to the reporter gene used for selection (false positives). Plasmids from those passing additional tests will be isolated and transformed into a fresh yeast strain to be sure the effects seen are not due to some mutation in the original yeast isolate. Finally, the inserts in the plasmids will be sequenced, and the sequences will be compared to the human genome to identify the genes of interest.

The reconstituted yeast system has several advantages. Yeast cells are easy to grow, and they grow quickly. Yeast cells do not encode any γ -secretase or APP proteins, so there will be no

interference in our assays from endogenous genes. The yeast activity assays are simple to perform. The β -galactosidase activity assays can provide quantitative data on γ -secretase activity. Finally, the established yeast system will allow for additional studies to identify additional proteins involved in altering γ -secretase activity.

Proposed One-Year and Long-Term Outcomes:

We anticipate that the work proposed herein will allow us to identify novel, human protein modulators of γ -secretase. It is also possible that we may identify genes with an association to AD that is not yet understood at the molecular level, allowing us to provide some insight. Using this methodology, we may identify novel AD-risk genes. Genomics has moved to the forefront of biomedical research. Many genome-wide assays have produced much data that is helping our understanding of many diseases. Our functional genomics study described here is the first step in the identification of novel AD-associated genes. Once identified, these genes will open the door to many exciting studies. These data will form the basis of an external grant application to the National Institutes for Aging and/or other institute or foundation as appropriate. It is possible that we may be able to publish the system as a methods paper in addition to publishing papers of data we obtain.

Year End Progress Summary:

We grew SH-SY5Y and U251 cells under normal conditions and in the presence of ROS. Total RNA was isolated from the cells. Although the RNA was of high quality, we were only able to synthesize cDNA from the RNA isolated from the cells grown under normal conditions. Currently, we are only proceeding with the cDNA we have though we anticipate attempting RNA isolation from cells treated with ROS, most likely changing the type of chemical being used.

One of the challenges we faced was the stability of one of our reporter yeast strains. Transforming DNA into the strain led to variable phenotypes even when transformed with empty vectors. We currently have stable strains to proceed with.

Our biggest challenge has been the library plasmid. The first plasmid that we constructed was not able to be transformed into the yeast strains. We have redesigned the plasmid.

We have cloned the γ -secretase subunits into single-copy yeast plasmids. This reduced the activity of γ -secretase on the C99-GAL4 target to the point where GAL4-reporter gene expression is not detectable, which will allow us to screen for γ -secretase activators. In addition to C99-GAL4, we are developing Notch1-GAL4 and N-cadherin-GAL4 targets to determine if effects we see are specific for C99 or more general for multiple γ -secretase targets. We have been able to detect both A β 40 and A β 42 using ELISAs to determine if any modulators can affect specific peptides being produced.

The work on this project will proceed beyond June 30. We will continue with the library preparation and screening.

The work on this project has been used in the training of a second-year master's degree student, a first-year master's student, and three osteopathic medical students.

Some of the preliminary data and ideas from this project have been used in a grant proposal to the state of Arizona: Arizona Department of Health Services, the Arizona Biomedical Research Centre (ABRC), Full Grant Application under RFGA2022-010.

ARIZONA ALZHEIMER'S CONSORTIUM
2021-2022 Scientific Progress Report

Regulation of neuronal gene expression by the telomere protection protein RAP1 and the demethylase TET3. Nancy S. Bae, PhD, Mark J. Swanson, PhD. Midwestern University; Arizona Alzheimer's Consortium.

Specific Aim:

Determine the effects of stress on neuronal cells and specific gene expression controlled by RAP1 and TET3.

Background and Significance:

Aging is a complex, inevitable, irreversible process characterized by the progressive, cumulative damage to cells and tissues within the body. Factors affecting aging include oxidative stress, telomere shortening, mutations, aggregation of proteins, etc. Many diseases arise with aging, such as heart disease, neurodegenerative diseases, and cancer. Though the mechanisms responsible for aging-associated pathologies are unknown, aging is presented as a genetically programmed developmental process. Other factors associated with aging are the accumulation of somatic mutations and reactive oxidation species (ROS), which leads to oxidative stress, accelerating cellular damage associated with aging. Telomere shortening and oxidative stress have been correlated to one another and connected to aging.

Telomeres are DNA structures found at the ends of eukaryotic chromosomes. They stabilize and protect the chromosome from end-fusions. When cells are not actively replicating, a six-membered protein complex called shelterin protects telomeres from damage and degradation. One subunit, RAP1 (repressor activator protein 1), is recruited to telomeres by TRF2 and is responsible for protecting telomeres from illegitimate recombination and thus maintains genome stability. Additional studies showed that RAP1 has functions independent of protecting telomeres. Our lab recently showed that under conditions of oxidative stress, RAP1 translocates to the cytoplasm. To understand the unique role(s) of RAP1 in the cytoplasm, a yeast two-hybrid screen was performed using RAP1 as a bait and a human fetal cDNA brain library as prey. We identified a specific isoform of the ten-eleven translocation gene family (TET), TET3, as an interacting protein of RAP1.

Epigenetic modifications of chromatin activate or suppress genes during development. These modifications include DNA methylation and histone modifications that alter transcriptional activity. DNA methylation is the addition of a methyl group to the 5-carbon of cytosine by DNA methyltransferases, producing 5-methylcytosine. DNA methylation is heritable, and methylated DNA is transcriptionally inactive, resulting in gene repression and chromatin organization.

TET enzymes are a family of dioxygenases that play a role in demethylation. There are three TET proteins, which all share the same catalytic activity. All three TET proteins can oxidize 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC) to 5-formylcytosine (5fC) or 5-carboxylcytosine (5caC). While TET1 and TET2 are found in embryonic stem cells, TET3 is predominantly found in neuronal cells where it plays a role in neuronal differentiation. Knockout of the TET proteins affects not only the 5mC levels, but it also results in telomere loss and chromosome fusion, indicating the TET proteins play a role in regulating methylation levels at telomeres. The repressor element 1-silencing transcription factor (REST) is involved in neuronal maturation. REST recruits TET3 to DNA for gene activation, but not TET1 or TET2, suggesting that TET3 and REST lead to gene activation in neuronal maturation. REST has been connected to cell death and Alzheimer's Disease (AD) in other experiments. Activation of autophagy in many age-related neurodegenerative disorders results in a destruction of cells in the body, which increases under stress. It was found that loss of REST in AD in the nucleus leads to autophagy. Treatment with H₂O₂ was performed to mouse cortical neurons. This led to a decrease in REST

levels, resulting in increased cell degeneration and cell death. When REST was overexpressed in H₂O₂ treated cells, oxidative damage was progressively reduced. This indicated that REST is important in cell protection and reduces oxidative stress during aging.

Neurogenesis creates new neurons from neuronal stem cells (NSCs). This consists of proliferation, differentiation, migration, and integration of cells. It occurs in the subgranular zone in the hippocampus and in the subventricular zone as well as in the amygdala. Dysregulation of neurogenesis in the subgranular zone has been related to cognitive deficits and memory loss in AD. Neuroinflammatory responses can also modulate adult neurogenesis. Neuroinflammation is one of the pathological hallmarks of Alzheimer's disease. It is characterized by microglial and astrocytic activation as well as the release of inflammatory factors. Such inflammation suppresses hippocampal neurogenesis. IL-6 is a major cytokine in the central nervous system that is known to participate in neurogenesis. Specifically, overexpression of IL-6 can induce astroglialogenesis, while inhibiting neurogenesis through the JAK2/STAT3 signaling pathway. The JAK2/STAT3 pathway regulated IL-6-induced TET3 expression, and the signaling inhibition stimulated DNA demethylation by suppressing TET3 expression in APP/PS1 mice. With diminished TET3 expression, there was markedly increased astrocytic differentiation and decreased neuronal differentiation in APP/PS1 mice compared to wild-type mice.

Oxidative stress, caused by buildup of ROS is a known component of the normal, cellular aging process. It is a key player in neurodegenerative disease such as AD. ROS accumulates during adult neurogenesis, causing the cells to differentiate along the astroglialogenesis pathway. In this way, glial cells are formed to protect the brain from ROS. However, too much astroglialogenesis may lead to astroglialosis and the subsequent onset of neurodegeneration and the development of Alzheimer's disease.

The research in this application will provide insight into the mechanisms of neurogenesis and astroglialogenesis that might contribute to the molecular mechanism of AD pathology.

Preliminary Data:

RAP1 and TET3 interact. The yeast two-hybrid (Y2H) system is a simple, yeast genetic method for detecting protein-protein interactions. Using the Y2H system, we identified TET3 as an interacting protein of RAP1. Using affinity tagged fusions of RAP1 and TET3 expressed from *E. coli* cells, we showed that the two proteins directly interact. By using fusions of various RAP1 domains, we determined that the myb domain of RAP1 is responsible for the TET3 interaction.

Target genes of RAP1 and TET3. Through an extensive literature search, we identified numerous target genes of RAP1 and of TET3, though no gene was tested for regulation by both proteins. For this project, we are focusing on five RAP1 target genes that are involved in neuronal development (RELN, CSRP1, H19, IGF2, HIC1) and one TET3 regulated gene that also affects neurons (NEUROD1). SH-SY5Y neuroblastoma and U251 glioblastoma cells were grown, and RNA was isolated. cDNA was made and subsequently mRNAs were analyzed using reverse transcriptase-quantitative polymerase chain reaction (RT-qPCR) to measure the gene expression. So far, we have validated primer sets for several target genes and the 18s and GAPDH primers as controls.

Experimental Design and Methods:

For the initial gene expression studies, we will continue to utilize both SH-SY5Y and U251 cells. Primer sequences were obtained from various published articles. The primers will be validated for the remaining target gene (RELN) while other primer sets for other genes (NeuroD1), (HIC1) and (IGF2) will be optimized or redesigned. Previously, we used specific levels of hydrogen peroxide (H₂O₂) to oxidatively stress U251 glioblastoma cells. In addition to H₂O₂, we will use tBHP (tert-butyl hydroperoxide) to induce oxidative stress to these cells. Cells will be grown under oxidative stress conditions, RNA will be isolated, and cDNA will be made. Once the genes are

tested under normoxic conditions, gene expression under oxidative stress will be tested to determine any changes. Both RAP1 and TET3 will be overexpressed in these cells, and the expression of the target genes will be compared. Changes in the gene expression profile due to either RAP1, TET3 or RAP1/TET3 overexpression compared to normal conditions will indicate novel roles for RAP1 in transcription regulation.

Neural stem cells can differentiate into neurons, or they can become glial cells to protect the brain. Human neural stem cells will be grown and differentiated to undergo neurogenesis. Astroglialogenesis will be induced using specialized media, and this will serve as a control for differentiation. Separately, neural stem cells will be treated with IL-6 or TNF- α to induce stress or H₂O₂ to induce oxidative stress. The gene expression of cells under each condition will be compared to determine the effects of differentiation on gene expression. The proteins from treated cells will be harvested, and immunoblotting will be done to determine whether the cells are undergoing neurogenesis or astroglialogenesis. Antibodies to NeuN will be used to determine which cells are undergoing neurogenesis. Antibodies to GFAP will be used to determine which cells are undergoing astroglialogenesis. The relationship between the RAP1-TET3 co-control of gene expression patterns will be investigated using RT-qPCR methods.

Proposed One-Year and Long-Term Outcomes:

We are using funds from the award to determine the effects of a telomere protein known to respond to oxidative stress on gene expression on the differentiation of adult neural stem cells through a demethylase that oxidizes methylated DNA. A balance between astroglialogenesis and neurogenesis in the adult brain is likely to be the key in protecting the brain and generating memories. Too much (oxidative) stress may lead to increased astroglialogenesis, possibly causing premature aging in the brain. We anticipate that this work will be the first in the field to provide an insight into the control of gene expression in the differentiation of neural stem cells in the adult brain with respect to its regulation by a telomeric protein. In addition, this project will be used to train two technicians and a master's degree student on the molecular mechanisms of Alzheimer's Disease.

Year End Progress Summary:

RNA from normal condition and H₂O₂ treated SH-SY5Y cells and U251 cells was isolated. RT-qPCR was performed on the RNA using primers targeting RELN, NeuD1, IGF2 and H19 mRNAs. Experiments were done four times. Though the trend of differential gene expression was noted, the fold increase/decrease differed from experiment to experiment. Of the four mRNAs, IGF2 and H19 gave the most consistent results, so we are continuing the studies with these genes. The next step is to isolate mRNA from cells in which RAP1 is overexpressed to see the gene expression pattern differences determining how RAP1 may be regulating TET3. We are expressing phosphor mutants of RAP1 to see how phosphorylation is affecting gene expression patterns of RAP1 and TET3 regulated genes.

Immunofluorescence was done on SH-SY5Y and U251 cells under the following conditions: endogenous RAP1, endogenous RAP1 with H₂O₂ treatment, overexpressed wildtype RAP1, overexpressed wildtype RAP1 with H₂O₂ treatment, overexpressed with RAP1 phosphor mutant (AAA), and overexpressed with RAP1 phosphor mutant (DDD). With H₂O₂ treatment and overexpression of RAP1, more RAP1 was present in the cytoplasm. The mathematical quantification is being done currently. With overexpression of phosphor mutants, RAP1 is being localized to the nuclear periphery as well as being found in the cytoplasm. RAP1 is making a ring around the edges of the cell. This would be in accordance with the fact that *S. cerevisiae* RAP1, a known transcription factor, is localized at the nuclear periphery. Both phosphor mutants show the similar patterns.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Reversal of western diet induced Alzheimer's-like pathology with genistein and/or exercise. Layla Al-Nakkash, PhD, Thomas Broderick, PhD, Minsub Shim, PhD. Midwestern University; Arizona Alzheimer's Consortium.

Specific Aims:

1. Determine ability of genistein and exercise to reverse Alzheimer's-like pathology in diabetic-obese mice.
2. Determine the impact of genistein and exercise to reverse senescence in diabetic-obese mice.
3. Determine the effects of genistein and exercise to reverse serum markers of diabetes and obesity in diabetic-obese mice.

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. Hippocampal neurogenesis is impaired following consumption of HFD, this is important since this region of the brain plays a role in learning and memory, specifically of flexible memory (the ability to use previously learned information in a new situation). 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. It has been postulated that, with such dietary habits, cognitive infirmarys are correlated with increased deposition of amyloid beta, increased formation of neurofibrillary tangles and reductions in synaptic plasticity. Clinically, overweight women are predisposed to cognitive dysfunction. Therefore, given the epidemic of obesity in the US, this proposed study is timely.

Although the adverse effects of obesity are well-known, its underlying mechanisms remain to be determined. For many chronic diseases including AD, aging is the greatest known risk factor. There is a connection between aging and cellular senescence, for example, the number of senescent cells increases with age in mammalian tissues with osteoarthritis and atherosclerosis. 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. Genistein is a naturally occurring isoflavonic phytoestrogen found in high concentrations in soy products. In our previous studies the optimal concentration of genistein we feed mice is 600 mg genistein/kg diet, which yields serum genistein levels of 4-8 μ M, akin to levels achievable in humans eating a diet containing a glass of soy milk daily. Thus, the concentration of genistein we use in our diet study is feasible clinically and causes no side effects in our murine studies. Importantly for this study, we have previously shown that this dose of genistein results in significant improvements in tissue function: jejunal chloride secretion (basal I_{sc}) is increased by a 4-week dietary genistein period in lean mice, and in ob/ob mouse jejunum. Genistein has been shown to alleviate neuroinflammation, amyloid beta deposition and to reduce oxidative stress in HFD-fed ApoE^{-/-} mice. It is reasonable to predict that genistein administration would have beneficial effects on systemic inflammation and gastrointestinal-brain health in the current study.

Exercise is commonly recommended by physicians to assist in reversing obesity. Of relevance to this proposal, exercise has been shown to improve hippocampal-dependent learning and memory in older individuals. Indeed, voluntary wheel running has been shown to ameliorate some of the memory dysfunction in HFD female C57BL/6J mice. From a cardiovascular perspective, there is some gathering evidence that AD is associated with risk of cardiovascular complication.

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 60 male *C57BL/6J* mice were purchased from Charles River Labs (aged 4-weeks), acclimated for 1-week, and then 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) for 12-weeks (HFHS diet induced diabetic obesity at 12 weeks). The mice were then randomly divided into 5 groups: HFHS, HFHS+genistein, HFHS+exercise, HFHS+genistein+exercise, Standard chow and regular water, and comparisons made to a group fed standard chow and water for the entire 24-week duration, i.e., lean controls (n=10/group). From time 13-24 weeks mice were assigned to one of those 6 groups. Genistein supplement was added to the HF diets (Dyets Inc, Bethlehem, PA) at a concentration of 600 mg genistein/kg diet. Importantly, we have found that this concentration of genistein incorporated in the diet is sufficient to produce significant beneficial modifications in intestinal function and bone health. Exercise duration 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). Comparison of sex-dependent effects and variances of mechanism(s) of action are fundamental to our long-term research objectives. Moreover, NIH guidelines require studies to utilize sex-dependent comparisons of animal models, thus proposing sex-dependent mechanisms, along with convincing preliminary data in future grant applications will be key. Mice were euthanized and tissues harvested and maintained at -80°C until use for these studies.

Proposed One-Year and Long-Term Outcomes:

We hypothesized that administration of genistein or exercise would improve outcomes in the HFHS-fed diabetic-obese mice. We predicted that both genistein supplementation combined with regular exercise would have additive beneficial effects. We predicted that we would reverse the detrimental effects of diet-induced obesity on cognitive dysfunction and AD-like pathology.

Year End Progress Summary:

Aim 1: Determine ability of genistein and exercise to reverse Alzheimer's-like pathology in diabetic-obese mice.

The assessment of brain pathology in our 12-week HFHS prevention study, took longer than anticipated. Therefore, we have not yet initiated this part of the study to assess potential reversal effects in the 24-week study and thus it falls into the 22-23 aims.

Aim 2: Determine the impact of genistein and exercise to reverse senescence in diabetic-obese mice.

We assessed p21 expression in colon and found no change in leans and HFHS fed mice and no subsequent changes with our treatments. In colon we noted a significant decrease in p21 expression with HFHS feeding versus leans and switching to standard diet/water reversed this.

In jejunum tissue, we found a significant increase in p21 expression in HFHS fed mice compared to leans and switching to standard diet/water, inclusion of genistein and genistein+exercise all reversed this. We found no change in jejunum p53 expression among the groups.

Aim 3: Determine the effects of genistein and exercise to reverse serum markers of diabetes and obesity in diabetic-obese mice.

We noted that HFHS diet significantly increase body weight (weight gain) and switching to stand diet/water and genistein+exercise together, significantly reversed this weight gain. Liver weight followed a similar trend to weight gain. Serum glucose levels followed the same trends.

We found significant increases in serum levels of TNF-alpha, MCP-1, Il-2 and Il-10 with HFHS feeding compared to lean controls. Switching to standard diet/water reversed levels of TNF-alpha, and MCP1 to that of leans. Inclusion of genistein in the HFHS diet reversed levels of TNF-alpha, to that of leans. Exercise reversed the HFHS induced increase in IL-10. Data indicates that removal of HFHS diet or inclusion of exercise has some beneficial effects on inflammatory cytokines.

Future grant applications, publications and collaborations that arose from the research:

Publications: one publication was published in April 2022, Oxidative Medicine and Cellular Longevity to address the influence of genistein and/or exercise on Alzheimer's related markers in the brain from our previous MAAC -funded 12-week HFHS genistein and/or exercise study "Effects of exercise and/or genistein treatment on high fat, high sugar diet-induced brain damage in C57BL/6 mice." Rongzi, Ding, Geetha, St Aubin, Shim, Al-Nakkash, Broderick and Babu. PMID: 35620577. This arose from a collaboration with Dr. Ramesh Babu at Auburn University.

The PI's (Al-Nakkash, Shim and Broderick) on the project have a second manuscript in preparation aiming to address the role of genistein and/or exercise on inflammation and senescence.

We are generating extramural grant aims based on the data to date.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Music Intervention in Occupational Therapy to Increase and or Maintain Quality of Life for Individuals with Dementia. Tamara Turner, EdD, OTR/L, Sarah Anderson, OTD, OTR/L. Midwestern University; Arizona Alzheimer's Consortium.

Specific Aims:

The manualized Music in Occupational Therapy Intervention will maintain Quality of Life (QoL) and reduce Behavioral and Psychological Symptoms of Dementia (BPSDs) for persons living with dementia as measured by the Quality of Life in Alzheimer's Disease (QoL-AD).

Background and Significance:

Dementia is not a normal part of the aging process but is commonly seen in the aging population. Often, individuals living with dementia feel a loss of control or an increase in the complexity to live their daily lives independently. The disease significantly affects a person's quality of life because individuals lose their independence to complete daily living activities or meaningful tasks by themselves. However, quality of life (QOL) is individualistic and may look different depending on what the person defines as meaningful (Alzheimer's Society of Canada, 2019).

The role of occupational therapy in promotion of health, wellbeing and QOL has been well documented (Pizzi & Richards, 2017). Occupational therapy should be included in every client's plan of care in order to support these goals. Due to the ever-growing older adult population, there is also a prevalence of cognitive impairments causing care providers to worry about the lack of resources and treatment options (Egan et al., 2018). Occupational therapists can provide resources and treatment options that are creative, individualistic, and holistic to provide the highest quality of care for these individuals. Occupational therapy needs to look deeper into nonpharmacological interventions that increase the QOL for persons living with dementia.

Nonpharmacological interventions, such as music therapy, have shown a positive effect on quality of life with dementia. It is a nonpharmacological tool that can be used in conjunction with other therapeutic activities to foster a more holistic treatment approach for individuals living with dementia (Dementia Australia, 2017.). Research has shown that music stimulates different areas of a person's brain that may help them connect with memories and express emotions, particularly when there is a personal connection (Dementia UK, n.d.). More specifically, involving recognizing familiar musical sounds, certain musical activities are maintained in individuals with dementia, showing promise for implementing music into therapy (Johnson et al., 2011). Music therapy employs a music therapist working with individuals or in a group setting to facilitate self-expression and communication and connection with others through music (Dementia UK, n.d). Music activities applied regularly have shown to be beneficial socially, cognitively, and emotionally for persons living with dementia (Särkämö et al., 2014). By improving the social, cognitive, and emotional abilities of people living with dementia through music, there is potential to improve the overall wellbeing of people living with the disease.

Preliminary Data, Experimental Design and Methods:

A systematic review "The Efficacy of Music Therapy Interventions on Quality of Life of Life for Individuals with Dementia" recently completed by Tamara Turner, Hallie Neale, and Katarina Bayer looked at the efficacy of music therapy interventions implemented in inpatient settings on increasing the QOL for individuals living with dementia. Music therapy interventions did show an increase in QOL; however this increase was not found to be statistically significant due to the heterogeneity of the studies.

These findings have multiple implications for occupational therapy practice. Based off the evidence from this systematic review the following recommendations are made for inpatient interventions targeting increased QOL for PWD:

- Hard to make specific recommendations as far as frequency and duration at this time, occupational therapy practitioners' can gather their own client data to make clinical
- Judgements
- Modify/adapt music therapy interventions based off stage seen with PWD due to progressive nature of disease
- In order to be occupation- based be sure to select music based off of each individual's "about me" information

Occupational therapy practitioners look at meaningful occupations to increase QOL, which could include using music therapy as an intervention and therefore should be further explored. Since there is a lack of treatment approaches for PWD, occupational therapy practitioners could incorporate active and passive music therapy to promote increased QOL and wellbeing for PWD. Although further research needs to be analyzed this is a start in the development of evidence-based interventions for PWD. As the need for long term care continues to rise, occupational therapists should consider contributing to effective strategies and EBP interventions to improve the QOL for individuals living with dementia.

With consultation from a Certified Music Therapist and in collaboration with student researchers, the faculty researchers will develop a manualized music intervention for persons living with dementia that occupational therapy practitioners can implement in practice.

It is planned to partner with a local Memory Care Facility or other dementia care agency in order to implement this program in the Summer 2021. Participants and carepartners will complete several assessments such as; the QoL-AD assessment, the Caregiver Assessment of Management Problems (CAMP), and the Mini Mental State Exam (MMSE), Slums. A Music Interest Checklist and the Adult/Adolescent Sensory Profile will also be completed by the patient/carepartner before beginning intervention in order to customize the program to meet each individual's needs. After completion of the program, researchers will survey the staff and managers of the memory care facility for feedback.

Proposed One-Year and Long-Term Outcomes:

- In one year, investigators will develop and locally implement described manualized intervention.
- In one year, investigators will analyze findings and disseminate knowledge via publications and conference presentations.
- In 2 years, investigators will refine further, as needed, the developed manualized intervention and implement its use in a state-wide study.
- In 5 years, investigators will refine further, as needed, the developed manualized intervention and make it available for use by all occupational therapy practitioners, so that it may be utilized state-wide and nation-wide.

Year End Progress Summary:

In consultation from a Certified Music Therapist and in collaboration with student researchers, the faculty researchers developed a manualized music intervention for persons living with dementia that occupational therapy practitioners can implement in practice. Musical instruments and portable wifi speakers were selected and purchased. Due to an unexpected leave of absence for the primary investigator, implementation of the intervention and data gathering has been delayed.

Study design is in review and once approved, investigators will proceed with implimenting the manualized intervention in local Arizona facilities. All 1-year outcomes are expected to be met within the next year.

**NORTHERN ARIZONA UNIVERSITY
PROJECT PROGRESS REPORTS**

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Investigating the mechanism of a dysbiotic gut microbiome dominated by *Bacteroides* in AD pathologies. Emily K Cope, PhD, J Gregory Caporaso, PhD, Jonathan Lifshitz, PhD. Northern Arizona University; Barrow Neurological Institute at Phoenix Children's Hospital; University of Arizona College of Medicine-Phoenix; Phoenix VA Health Care System; Arizona Alzheimer's Consortium.

Specific Aims:

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). Our prior studies have demonstrated a temporal increase in the relative abundance of the bacterial genus, *Bacteroides*, in the GI tract of mice exhibiting amyloid pathologies (3xTg-AD and APPPS1). However, it is unclear whether increased relative abundance of *Bacteroides* is a result of amyloidosis or drives plaque deposition. *The central hypothesis governing this proposal* is that *Bacteroides* spp. contributes to more severe AD pathologies by driving a neurotoxic inflammatory milieu. To address this hypothesis, we propose the following Specific Aims:

Specific Aim 1. Characterize the *Bacteroides* species within the GI tract of 3xTg-AD and wild-type B6129SF2/J mice leveraging previously sequenced fecal, colon, and cecum samples. *We hypothesize that higher resolution amplicon analysis and shallow shotgun metagenomics will identify 1-2 species within this genus that are predictive of age and strain.*

Specific Aim 2. Determine the role of *Bacteroides* spp in neuroinflammation, amyloidosis, and cognitive function in 3xTg-AD and wild-type B6129SF2/J mice. *We expect that findings from this study will determine a role for a predominant GI microbial community member in driving neuroinflammatory processes, potentially leading to cognitive impairment and more severe amyloidosis in mice predisposed to AD pathologies.*

Background and Significance:

The gut microbiota-brain axis is highly relevant in AD. Gut microbiota influence neurological health through production of immunomodulatory metabolites, direct interaction with the immune system, and stimulation of the vagus nerve or enteric nervous system.¹ Changes in gut microbiota composition and diversity during aging can drive age-associated inflammation; recent studies in *Drosophila*² and in murine models^{3,4} suggest that alterations to the gut microbiota in late life drive intestinal permeability and increased systemic inflammatory markers. Since neuroinflammation is a key feature of Alzheimer's Disease (AD), understanding the aging gut microbiome is critical to understanding AD progression. Mechanistically, bacteria in the GI tract can produce significant amount of amyloids (aggregated, insoluble proteins exhibiting β -pleated sheet structures), LPS, or other pro-inflammatory metabolites that can prime the immune system during aging, contribute to amyloidosis, and increase the risk for AD.⁵⁻⁷

A fundamental biological property of all life forms, including microorganisms, is their rate of growth. Rare populations with high growth rates may have substantial impact on metabolic processes in the GI tract. Our understanding of microbial functioning in the GI tract largely rests on the abundance of DNA or RNA sequences, some of which may turn over very rapidly while others persist for extended periods of time. To measure the turnover of DNA sequences in the murine GI tract, an isotopically substrate, ¹⁸O-water, can be traced into nucleic acids. Using this technique (quantitative stable isotope probing, or qSIP) taxon-specific microbial growth rates can be calculated to better understand microbial processes in the GI tract.^{8,9} In environmental microbiology, qSIP has been successfully applied to understand growth rates of bacteria and

fungi in grasslands¹⁰ and freshwater ecosystems.¹¹ However, qSIP has not been widely used to understand the microbial ecology of the GI tract in biomedical research.

Our proposed study addresses important limitations of prior research in the nascent field of gut microbiota-brain interactions relevant to AD. Recent studies of the gut microbiota in different strains of mice genetically prone to AD demonstrate altered gut microbiota composition compared to wild type mice.¹²⁻¹⁴ There have only been five studies published on gut microbiome alterations in AD in humans.¹⁵⁻¹⁹ Each study demonstrates a change in relative abundance of *Bacteroides* in individuals with AD pathologies. However, there is no consensus of specific species that are enriched in AD or models of AD pathology, and still no consensus on potential mechanisms mediated by the gut microbiome. **Completion of this innovative project will result in a better understanding of the role of distinct host-associated microbiota in AD progression and neuroinflammation.**

Preliminary Data, Experimental Design and Methods:

Gut microbiota alterations in a murine model of AD. With support of the AAC, we have recently analyzed the gut microbiota of wild-type B6129SF2/J (i.e., genetic control) and 3xTg-AD mice to determine whether there are unique temporal gut microbiome signatures of AD progression. Fresh fecal pellets were collected fortnightly for 52 weeks bacterial microbiome analysis. We observe striking differences in the abundance trajectory of gut microbiome taxa between our wild-type and 3xTg-AD mice over time. Gut microbiome composition in our mice changes predictably with time, such that using Random Forest machine learning regressors we can accurately predict the week that each sample comes from given only its microbiome composition (r-squared: 0.49; p=0.000002).^{20,21} These Random Forest models identify specific taxa that are changing with progression of 3xTg-AD mice through disease. *Bacteroides* sp. in relative abundance over time in 3xTg-AD mice but not wild-type mice, and therefore may be a potential indicator that they may be drivers of AD progression. Other common GI taxa do not change over time between the strains (e.g. *Lactobacillus*).

In vivo quantitative stable isotope probing to quantify microbial growth and death rates. As proof of concept, we used qSIP to quantify microbial growth rates in the murine GI tract (fecal and cecum). Mice were dehydrated for 24h and then maintained on either isotopically enriched (98 atom% ¹⁸O-water) or ¹⁶O-water for 48h. DNA was extracted from harvested tissues and nucleic acids were separated on a cesium chloride gradient via ultracentrifugation. Nucleic acids from mice maintained on ¹⁸O-water were, on average, more dense than nucleic acids from mice fed ¹⁶O-water, indicating that the ¹⁸O stable isotope was successfully incorporated into the actively dividing microbial community members. Top growers in both the cecum and fecal samples were classified as *Clostridiales* and *Lachnospiraceae*, known fiber fermenters. The highest microbial growth rates (positive ¹⁸O fragment excess), and the greatest number of growing microbial taxa, were observed in the cecum where especially the *Clostridiales* grew rapidly. Though the *Lactobacilli* comprised a substantial proportion of the 16S rRNA sequences, their nucleic acids were not enriched in ¹⁸O, indicating they grew little. The observation that the *Lactobacilli* were not replicating in the murine GI tract could only be made through qSIP and could not be obtained through standard sequencing approaches.

Experimental Designs and Methods:

Specific Aim 1. We will use two approaches to resolve *Bacteroides* species, leveraging previously collected amplicon and shallow shotgun metagenomic sequence data. We will use q2-clawback (co-developed in MPI Caporaso's Lab)²² to assemble empirical species-level taxonomic distributions based on shallow shotgun metagenome sequencing results; these taxonomic

weights will inform the naive Bayes taxonomy classifiers implemented in q2-feature-classifier to improve species-level classification of amplicon sequence data. Using this improved taxonomic classification, we will perform Random Forest analysis to predict age+strain. We will also perform differential abundance testing using available methods at the time of analysis, such as ANCOM²³ or Songbird.²⁴

Specific Aim 2. Mice will be challenged with oral gavage of up to three *Bacteroides* species (10^{4-6} CFU in 100 μ L) that were highly predictive of 3xTg-AD mice in our Random Forest model employed in Specific Aim 1. As a control, we will also give oral *Lactobacillus* (10^{4-6} CFU in 100 μ L). Because antibiotic perturbation to the gut microbiota can independently impact AD pathologies,^{25,26} *Bacteroides* and *Lactobacillus* will be administered with and without pretreatment with an antibiotic cocktail to perturb the gut microbiome (ampicillin, vancomycin, neomycin, gentamycin, and erythromycin).²⁵ **The following experimental groups will be included for both 3xTg-AD and B6129SF2/J wild-type mice (6 mice per strain, n=144 mice total):** **1)** no antibiotic cocktail, oral PBS, **2)** antibiotic cocktail, oral PBS, **3)** no antibiotic cocktail, oral *Bacteroides spp.*, **4)** antibiotic cocktail, oral *Bacteroides spp.*, **5)** no antibiotic cocktail, oral *Lactobacillus spp.*, **6)** antibiotic cocktail, oral *Lactobacillus spp.* Fecal pellets, blood, and cerebrospinal fluid (CSF) will be collected longitudinally. Mice will be sacrificed at 8 weeks (baseline), 24 weeks (amyloidosis), and 52 weeks (tauopathy). At sacrifice, mice will be euthanized and tissue sections will be collected for molecular analysis (stored in RNAlater) and IHC (immediately fixed in aldehydes). **qSIP Methods:** We will implement qSIP four days prior to each timepoint. Mice will be dehydrated for 24h, then allowed access to ¹⁸O (labeled) or ¹⁶O (unlabeled) water *ad libitum*. Extracted DNA will be separated by density, or ¹⁸O composition, on a cesium chloride gradient formed in an ultracentrifuge. **Microbiome Sequencing:** For 16S rRNA gene sequencing, the universal primers 515F and 806R will be used to amplify the V4 region as previously described.^{27,28} Amplicons will be sequenced on the Illumina MiSeq platform. **Neuropathology and inflammatory response.** We will use reverse transcriptase qPCR to measure inflammatory gene expression. Markers for Th1/Th17, astrocyte reactivity, and M1/M2 macrophage activation/microgliosis will be included.^{29,30} We will quantify A β deposition, tauopathy, microgliosis, and reactive astrocytes using IHC. Consultant Lifshitz will advise on analysis to quantify microglia deramification (activation).^{31,32} **Additional outcomes as resources allow.** Behavioral and cognitive assessments will be performed at each timepoint (8, 24, and 52 weeks) in collaboration with AAC consortium members (TBD). CSF will be collected to quantify pTau, neurofibrillary tangles (NFTs), and other relevant biomarkers. LPS will be quantified in serum and brain homogenate via ELISA.

Proposed One-Year and Long-Term Outcomes:

These studies will be the first to assess the role of a gut microbiome characterized by predominance of *Bacteroides* in driving AD pathologies. The work proposed here is a logical extension of our prior AAC-supported findings. We expect to identify relevant *Bacteroides* species within the first quarter, and will complete the interventional arm of the study within one year. As a result of our funding in the AAC, we have submitted three proposals to the NIH/NIA, Alzheimer's Association, and the Infectious Disease Society of America. A recent R21 to PAR-19-071, the goal of which is to develop a qSIP to study microbiome dynamics in the GI tract of 3xTg-AD mice, scored in the 11th percentile (NIA payline is 28th percentile). A fourth year of funding will support an R01 to the NIH and we have identified a relevant funding opportunity that has several notices of special interest that fit our program of study: PAR-19-070 (*Research on current topics in AD and related dementias*). We expect that the results from this fourth year of funding would lead to an additional high-impact publication.

Year End Progress Summary:

Progress made toward one-year outcomes.

Specific Aim 1. We will use two approaches to resolve *Bacteroides* species, leveraging previously collected amplicon and shallow shotgun metagenomic sequence data.

We have completed shallow shotgun metagenomic sequencing from a longitudinal cohort of 3xTg-AD and wild-type B6129SF2/7 mice at three key timepoints related to disease progression (8 weeks representing baseline, 24 weeks representing amyloidosis, and 52 weeks representing amyloidosis and tauopathy, n=120 carefully selected fecal samples). Raw sequence data were removed of host DNA using Bowtie2, and species and strain-level taxonomic assignment was performed using Kraken2 and Braken 2, respectively. Subsequent feature tables were imported into QIIME2 for analysis. We are currently integrating q2-clawback into these analyses for even more accurate species and strain-level characterization of the gut microbiome. Using this high-resolution approach, we identified several species of *Bacteroides* that were differentially enriched in 3xTg-AD or wild-type mice. Further, these results confirm that the abundance of beneficial *Lactobacillus* spp is greater in wild-type mice, which we had previously observed using 16S rRNA gene sequencing. Importantly, *Lactobacillus* is difficult to characterize to the species level using the V4 region of the 16S rRNA gene. Using shallow shotgun metagenomics, we found that *L. johnsonii* is associated with healthy, wild-type mice over time (r-squared 0.75, p=0.002).

A major goal was to identify species of *Bacteroides* to use in the experimental Aim 2. We found that *B. thetaiotaomicron* was enriched in healthy wild-type mice. *B. thetaiotaomicron* is a prominent member of the healthy human and mouse gut and can regulate colonic innervation and neuronal function, and thus, is likely critical to the healthy gut microbiome-brain axis.¹ We observed enrichment of *B. caccae* in 3xTg-AD mice and a stronger signal of *B. fragilis* in 3xTg-AD mice compared to control mice. Although at a low abundance, *B. fragilis* was intriguing to investigate because although *B. fragilis* has been demonstrated to affect the gut microbiome-brain axis (in a positive way) in autism spectrum disorder,² this species is postulated to contribute to neuroinflammation in AD via secretion of metabolites and LPS in the gut, contributing to amyloidosis in the gut and brain.³⁻⁵

Specific Aim 2. Determine the role of *Bacteroides* spp in neuroinflammation, amyloidosis, and cognitive function in 3xTg-AD and wild-type B6129SF2/J mice.

We have completed the first two timepoints (8 week and 24 week, n=12 mice/strain). 3xTg-AD and wild-type mice were bred and dosed with 10⁹⁻¹⁰ colony forming units (CFUs) of *B. fragilis* or *L. johnsonii* in an applesauce mixture as previously described.² We implemented qSIP four days prior to each timepoint (8 and 24 weeks). Mice were dehydrated for 24h, then allowed access to ¹⁸O (labeled) or ¹⁶O (unlabeled) water *ad libitum* for 72 hours prior to sacrifice. Terminal fecal, cecum, ileum, hippocampus, frontal cortex, and CSF samples were obtained from each mouse. Extracted DNA was separated by density, or ¹⁸O composition, on a cesium chloride gradient formed in an ultracentrifuge. This will allow us to quantify growth dynamics in the fecal microbiome over time. We have performed 16S rRNA gene sequencing on each of the 22 gradients isolated from each fecal sample. Implementation of qSIP will allow us to compare growth rates of *B. fragilis* and *L. johnsonii* associated with disease progression. The following year of AAC funding will allow us to evaluate the invasion and colonization dynamics of *B. fragilis* and *L. johnsonii* at 52 weeks.

Progress made toward long-term outcomes.

Support from the Arizona Alzheimer's Consortium has resulted R21 funding to adapt a novel technology that is widely used in environmental microbiome sciences, quantitative stable isotope probing (qSIP), to further understand gut microbiome dynamics and relationship to Alzheimer's disease progression and neuroinflammation. We have a manuscript under review at Scientific Reports that demonstrated the power of dense microbial sampling in longitudinal studies of the gut microbiome in mice modeling AD pathologies, and that the gut microbiome accurately

predicts neuropathologies at pre-pathology timepoints (pre-print <https://doi.org/10.21203/rs.3.rs-1538737/v1>).

Future grant applications, publications, and collaborations.

The National Institutes of Health National Institute on Aging has recently announced a new FOA on the Impact of the Gut Microbiome-Brain Axis on Alzheimer's Disease (PAR-22-211). We are preparing to submit an R01 to this new mechanism to further our understanding of the mechanisms underlying the role of the gut microbiome in AD. We are also preparing a manuscript for submission to mSpectrum (a journal from the American Society for Microbiology) that demonstrates partial engraftment of the fecal microbiome and *Bacteroides* enrichment in mice receiving fecal microbiome transplants from aged 3xTg-AD mice. Finally, the Arizona Alzheimer's Consortium has connected NAU and our research group with scientists from diverse disciplines, and we intend to continue these collaborations and expand beyond them in the next year of funding. Prior years have added neuroimmunology expertise (Jonathan Lifshitz, PhD), expertise in the 3xTg-AD model (Roberta Brinton, PhD), expertise in quantitative stable isotope probing (Egbert Schwartz, PhD) and expertise in behavioral analysis (Carol Barnes, PhD). We expect that the next year of funding will increase our collaborations to include metabolomics (TBD).

References:

1. Aktar, R. et al. Human resident gut microbe *Bacteroides thetaiotaomicron* regulates colonic neuronal innervation and neurogenic function. *Gut Microbes* 11, 1745–1757 (2020).
2. Hsiao, E. Y. et al. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell* 155, 1451–1463 (2013).
3. Lukiw, W. J. *Bacteroides fragilis* Lipopolysaccharide and Inflammatory Signaling in Alzheimer's Disease. *Frontiers in Microbiology* vol. 7 (2016).
4. Sun, F. et al. A potential species of next-generation probiotics? The dark and light sides of *Bacteroides fragilis* in health. *Food Res. Int.* 126, 108590 (2019).
5. Zhao, Y., Jaber, V. & Lukiw, W. J. Secretory Products of the Human GI Tract Microbiome and Their Potential Impact on Alzheimer's Disease (AD): Detection of Lipopolysaccharide (LPS) in AD Hippocampus. *Front. Cell. Infect. Microbiol.* 7, 318 (2017).

**TRANSLATIONAL GENOMICS RESEARCH INSTITUTE
PROJECT PROGRESS REPORTS**

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

MindCrowd: Development of additional internet-based cognitive tasks and enhanced recruitment of underrepresented minority groups. Matt Huentelman, PhD, Lee Ryan, PhD. Translational Genomics Research Institute; University of Arizona; Arizona Alzheimer's Consortium.

Specific Aim(s):

We have two specific aims for our proposed work as follows:

- 1) Specific Aim 1: Develop an expanded battery of cognitive tasks within MindCrowd.
- 2) Specific Aim 2: Increase recruitment of underrepresented minority groups into MindCrowd.

Background, Significance, and Preliminary Data:

MindCrowd is an internet-based research study that we collaboratively launched in January of 2013. The current version of the study site includes the collection of ~25 demographic, health, lifestyle, and medical questions as well as the administration of two tasks – a simple visual reaction time task and a paired associates learning task. During the past 8 years, participation in MindCrowd has grown to over 225K individuals from over 150 countries around the world. In 2020, we contracted with a marketing firm in Atlanta to specifically enhance recruitment of underrepresented minority groups with a focus on Latino individuals of all races, Black / African Americans, and individuals of mixed race. We were successful in these efforts, effectively increasing the recruited percentages by over 200% for the first two groups and over 600% for individuals of mixed race. Research study of these typically understudied groups is critical to make informed and accurate inferences regarding the factors associated with the aging brain. During the execution of the proposed efforts for FY2022, we plan to continue to enhance recruitment of these underserved groups and further explore novel ways to recruit additional facets of the general population into MindCrowd. Additionally, we will develop a new version of the MindCrowd site that will administer eight additional tasks via the internet. These tasks will expand the number of cognitive domains studied within MindCrowd and by extension the breadth of brain performance that we are able to characterize in our study participants.

Experimental Designs and Methods:

For Specific Aim 1: We have already designed computerized versions of the following tasks: simple visual reaction time, verbal paired associates, face-name associates, object recognition, letter-number sequencing, keep track, flanker, object discrimination, and complex reaction time. During the next six months these tasks will be coded and adapted for web-based administration as part of the MindCrowd infrastructure. Tasks will then be alpha and beta tested in laboratory staff and then in a targeted focus group. At the conclusion of the development and testing, we will launch these tasks for participation by those in MindCrowd who have provided name and contact information as well as consented for re-contact regarding future research.

For Specific Aim 2: We have already designed electronic-based recruitment campaigns that result in the enhanced recruitment of Latino, Black / African American, and mixed race individuals. We will continue to execute these campaigns but also refine and improve our efforts. This will entail paid campaigns on Twitter and Facebook as well as Google Ads. Additionally, we will continue our recruitment efforts via monthly newsletters and blog posts relating to topics of interest in the areas of brain health, aging, and dementias.

Proposed One-Year and Long-Term Outcomes:

For Specific Aim 1: (1) launch site with increased selection of cognitive tasks, (2) recruit 1,000 or more individuals to participate in these new site, and (3) submit national conference abstract on these results.

For Specific Aim 2: (1) achieve 12% Latino, 5% Black / African American, 5% mixed race participation in MindCrowd during FY2022 [July '21 – July '22], (2) submit a publication on the Latino-specific MindCrowd results, and (3) submit a publication on Latino-specific recruitment efforts and results.

Long-Term Outcomes: We expect to grow the cohort who participates in the expanded cognitive task battery in a similar fashion as we have with the main MindCrowd site. We expect to recruit 5,000 individuals each year into this expanded site. Additionally, we will institute longitudinal testing of the cohort as well with an interval of 12 months. These efforts – combined with our work with underserved minority groups – will be utilized to compete for Federal grant funding in the coming years.

Year End Progress Summary:

Specific Aim 1: Develop an expanded battery of cognitive tasks within MindCrowd. Our goals were as follows; (1) launch site with increased selection of cognitive tasks, (2) recruit 1,000 or more individuals to participate in the new site, and (3) submit national conference abstract on these results. We completed the development of the new site with the expanded selection of tasks. It was launched on June 16th. To date we have had ~3,000 participants join the new site and ~100 of them have completed three or more tasks. The launch and therefore recruitment was slightly delayed and therefore our total number of participants is less than expected at the time of this progress report, therefore, we have not yet submitted the abstract on our findings to a national conference. However, we plan to do this before the end of this year once we reach the 1,000 participant milestone.

Specific Aim 2: Increase recruitment of underrepresented minority groups into MindCrowd. Our goals were as follows; (1) achieve 12% Latino, 5% Black / African American, 5% mixed race participation in MindCrowd during FY2022 [July '21 – July '22], (2) submit a publication on the Latino-specific MindCrowd results, and (3) submit a publication on Latino-specific recruitment efforts and results. During this period we achieved 8.2% Latino, 3.3% Black / African American, and 3.4% mixed race participation. These levels are lower than our goals however they are higher than the historical rates within MindCrowd, therefore, we believe that our recruiting efforts are improving our recruitment in these race-ethnic groups. Unfortunately because the new site launch was delayed until June we were unable to measure the effects of the new site on the recruitment of these groups, and we predict that the nature of the new site – and its ability to be joined on smartphones – will dramatically further improve our recruitment. The two publications are still being drafted, however, we expect them to be submitted before the end of this calendar year.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Single cell profiling of blood-brain barrier in COVID-19 cases. Kendall Van Keuren-Jensen, PhD, Nadine Bakkar, PhD, Thomas G. Beach, MD, PhD. Translational Genomics Research Institute; Barrow Neurological Institute; St Joseph's Hospital and Medical Center; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

Aim 1. Single cell sequencing and analysis of brain microvasculature in patients with Alzheimer's disease and SARS-CoV-2 compared to infected individuals without Alzheimer's disease.

These data were to establish the changes COVID had on patients with Alzheimer's disease compared to COVID changes in the BBB of individuals without Alzheimer's disease

Aim 2. (added during the year) Single cell sequencing and analysis of brain microvasculature in neurologically normal controls, Alzheimer's disease and vascular dementia

We added these groups for comparing BBB changes associated with COVID (Aim 1) to individuals that did not have COVID; nondemented controls, individuals with Alzheimer's disease, and individuals with vascular dementia.

To our knowledge no one has compared these different groups to one another using 10x single nuclei data from enrichment of blood vessels in the brain.

Background and Significance:

The blood-brain barrier (BBB) is comprised of endothelial cells, astrocytes, and pericytes and is essential for transporting oxygen and nutrients to the brain, while protecting it from toxins. If the BBB is disrupted, this would lead to increased inflammation and a lack of nutrients and oxygen to the brain. Our hypothesis is that dysfunction of the BBB can occur during SARS-CoV-2 infection, leading to reduced oxygen and nutrient supply to the brain and creating difficulties with thinking and attention (brain fog). In addition, we hypothesize that BBB dysfunction caused by SARS-CoV-2 infection can exacerbate cognitive problems in neurodegenerative disease. We will test this by comparing nondemented controls (COVID positive) to Alzheimer's patients (COVID positive).

During the year, we expanded our investigation of the changes in BBB cell types to include nondemented (COVID negative) individuals as well as subjects with Alzheimer's disease (COVID negative) and individuals with vascular dementia (COVID negative). We hope to identify transcriptomic changes in cells due to viral infection as well as changes related to disease. We would then like to follow this up in the future with models of the BBB to assess how these transcriptomic changes impact function; movement of nutrients, oxygen and waste into and out of the brain. Given the number of different groups and the potential unique and overlapping changes in the cells of the BBB across these groups, we believe we have a very unique and informative dataset for understanding transcriptomic changes associated in the cells of the BBB that exacerbate cognitive deficits.

To investigate whether or not the BBB has undergone changes leading to cellular dysfunction due to virus infection, disease or injury, we used a recently described approach to assess the vasculature of the brain using single cell sequencing (Yang et al., 2021; PMID: 35165441). Researchers developed Vessel Isolation and Nuclei Extraction for Sequencing (VINE-seq). This single cell approach will allow us to enrich for the relevant cell types and investigate involvement of each cell type and its potential dysfunction associated with COVID-19 infection, and dementia – related to Alzheimer's disease and known vascular disturbances. We will sequence samples from the following groups 10 COVID positive nondemented individuals, 10 COVID negative nondemented, 10 COVID positive Alzheimer's, 10 COVID negative Alzheimer's and 10 individuals with vascular dementia.

In a related proposal, Dr. Bakkar at BNI will examine the BBB at the single cell level, using VINE-seq, in patients with several dementias (FTD, LBD and AD) compared with controls. Dr. Bakkar will examine the vasculature from 4 LBD, 4 FTD-TDP43 and 4 control patients.

Preliminary Data, Experimental Design and Methods:

The bulk of the year was spent improving methods based on VINE-Seq (Yang et al. 2021; PMID: 35165441). We worked to establish methods here at TGen in collaboration with Nadine Bakker at BNI. Because the bulk of the time was spent maximizing this protocol for blood vessel/cell enrichment, we will describe the protocol we are currently using:

1. Vessel isolation: Place brains on ice (> 0.7g material). Add 1ml of thawing buffer (1% BSA with RNase; 1:200) plus protease inhibitor (1:25) to a 35 mm dish with tissue. Mince into 1mm pieces with two scalpels. Try to get the pieces as small as possible. Move the tissues to the homogenizer, add another 1ml buffer to wash the plate. Dounce minced tissue with 2 ml dounce. Add it to a 50ml conical containing 25ml Dextran. Mix well (invert to visually see the mixing and then vortex for 10s). Spin at 4C, 4,500g for 18' w/ 1 on the brake (swinging bucket centrifuge). There will be three layers, A) the top - myelin (very fatty and thick), B) middle - parenchymal layer, C) bottom blood vessels. Aspirate the myelin layer with P1000, with a swirling motion to make it stick to the pipet tip. Switch to a 5ml serological pipet and aspirate the parenchymal supernatant. Leave around 500ul on top of the blood vessel pellet, resuspend the pellet in 1ml of 1% BSA in PBS.

2. Cell liberation from vessels: Wet 40 µM strainer atop 50ml falcon tube with 5ml of 1% BSA. Apply vessels in the center of a 50ml falcon with 40 µM strainer cap. Wash with 35ml of cold PBS. Wash next with 10ml of cold 0.32M sucrose. After 50ml, flow through should be unimpeded—if still blocked, repeat wash step. Typically only needed additional wash steps in > 1.5g of starting material was used. Switch filter onto a new 50ml Falcon tube (throw away prior 50ml tube). Press and rotate the rubber end of a 3ml syringe plunger on strainer (5 grind steps total). Can be more firm in force applied with each step. Collect with 5ml of 0.32M sucrose. Repeat grinding and add another 5ml of 0.32M sucrose. Repeat grinding. Collect with 5ml 1%BSA. Repeat grinding. Collect with 5ml 1%BSA. Final collection with 30ml of 1% BSA in PBS. Pellet material in 50ml collection falcon tube by spinning 1,000g 4C 10'. Quality check: check for nuclei liberation from vessels and cells on the countess at this stage. Resuspend samples in 4 ml of EZ nuclei lysis buffer.

3. Prepare for FACS: Triturate samples with pipet tip. Incubate on ice for 10 minutes, swirling at the 5' mark. Spin down 500g 5', (in FACS tube). Add 500ul 1% BSA, wait 2 min (do not mix), then add another 500ul and resuspend. Debris cleanup &

4. Prepare for sorting: Spin down 500g for 5min. Resuspend in 500 µL of 2% BSA (+ 1:200 RNase inhibitor). Check on the Countess again to see the concentration (use NucBlue). Aim for 1-2 million cells in 500ul to go on the FACS sorter.

5. Prepare for 10x: Once samples have gone through the sorter, they are clean and ready for injection on the 10x instrument.

This method resulted in a >10 fold increase in CD31, also known as platelet endothelial cell adhesion molecule 1. We have acquired a robust protocol for isolating blood vessels and we are finishing processing and analyzing samples.

Proposed One-Year and Long-Term Outcomes:

We plan to complete analysis of this data and submit a publication. This is a significant examination of cells that make up the BBB across a number of diseases and infections. We will learn about deregulated pathways in different cell types and we will try to model these changes in iPSC systems. We will apply for additional funding to pursue these functional studies as well as additional studies to look at more granular information, such as genetic and environmental changes that may contribute to changes in BBB and disease. Our collaboration with Dr. Bakker

resulted in her writing an R21. We plan to write a grant to continue this data analysis, as well as to look at how these transcriptional changes lead to altered function of the BBB.

Year End Progress Summary:

We spent a large amount of time getting our methods worked out for these studies, to enrich for blood vessels and then dissociate the cells that make up the BBB. We have a working protocol, described above. We have also been working on an analysis pipeline for our single nuclei data. We expanded the current study to include non-COVID subjects, Alzheimer's patients, as well as patients with known vascular dementia. We have received the additional tissue and we have been processing the samples through sequencing. We will continue with the analysis and the drafting of a manuscript.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

A CRISPR knockout negative screen to identify genes that lead to enhancement of efficacy of antibodies targeting amyloid beta (A β) 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 Aims:

The specific aim of this project is the identification of genes that interact with the efficacy of the antibodies targeting amyloid β (A β) 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 A β peptides, we will identify genes that influence the expression of A β and P τ 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 (A β) 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 A β 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 A β peptides in the brain [3]. Recruiting the immune system may prevent A β peptides from clumping into plaques or remove A β plaques that have formed and help the body clear the A β peptides from the brain. Reducing these plaques by means of passive or active vaccination against A β 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 A β 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:

During the past year we established fresh growing cultures of NPC derived from Alzheimer's disease's patient and healthy donors. Established NPC were then induced toward neuronal differentiation for 4-5 weeks, followed by maturation process to adult neurons for 4-6 weeks. To confirm maturation, we performed qPCR for expression of adult neuronal markers MAP2 and Beta III Tubulin at 4- and 6-weeks post-maturation initiation process. At 4 weeks we observed a 3 folds increase of MAP2 expression, but not significant increase of Beta III Tubulin was detected. At week 6, MAP2 and Beta III Tubulin expression increased by 7 and 3 folds respectively, suggesting that the neurons reached full maturity and were ready for assay testing.

Mature neurons from AD patient and healthy donor were then tested for hyperphosphorylated Tau Th231 expression by SD-PAGE western blot. Briefly, mature neurons were seeded in T25 laminin-coated flask and growth to 70% confluency with medium change every 3 days for maintenance. At the required confluency, neuron cultures were treated with Accutase for 5 min at 37 C and the harvested cells were washed with PBS followed by lysis with RIPA buffer for 20 min in ice. Lysates were resolved in SDS-PAGE gels and PTau Thr231 detected by western blot. Our results showed significantly high levels of PTau Thr231 expression in neurons derived from AD patients compared to the same protein expression in neurons derived from healthy donors.

To optimize the protocol assay for the reading of the CRISPR screening and Kinase library screening, we evaluated the expression of PTau Thr231 in AD patient-derived mature neurons in comparison to the healthy donor in a 384-well plate format by performing in cell western blot as originally suggested in the grant proposal. Unfortunately, detection of PTau Thr231 levels in this format is very difficult due to the low sensitivity of the antibody for Th231 and the Lycor Odyssey instrument used for the assay. To solve this issue, we opted to analyze the levels of PTau Thr231 by using the multiplexed immunoassays ELISA (Meso Scale Discovery), a very sophisticated ELISA platform routinely used in our laboratory that allows precise and accurate analysis of phosphoprotein a >pg levels. The Phospho(Thr231)/Total Tau Kit provides assay-specific components for the quantitative determination of phospho-tau (Thr231) and total tau in human neuron lysates and tissue culture supernatants. Preliminary results shown MSD multiplex plates able to detect PTau Thr231 levels from the 384 -well plate format that will be used in the screening, and the same technology can be also used to detect A β 42 levels from the neurons conditioned medium, thus we suggested a change in the grant proposal protocol.

We also optimized the neuron transfection protocol to use for the CRISPR screening. Transfection of primary cells, including neurons, is difficult and often unsuccessful due to the low dividing rate of this type of cells. Nucleofection is usually the favorite option, however it is not applicable in our CRISPR platform. We performed several tests in which we used different transfection reagents on mature neurons derived from AD patients and healthy donors. To assess the efficacy of the transfection we use GFP expression as control. Our data showed that Lipofectamine MessengerMAX mRNA Transfection Reagent delivers high transfection efficiency in neurons. In the next step, we will assay the optimum ratio sgRNA:CAS9 for our CRISPR transfection by knocking down a housekeeping gene as control and assessing the expression by qPCR and western blot. Lastly, it is well known that A β plaque formation results in increased inflammation associated to expression of inflammatory cytokines, including IL-1 β . Increased inflammation levels promote activation of kinases responsible for the activation of Tau protein kinase 1, leading to the hyperphosphorylation of tau. To identify potential treatments that can be used in combination with antibodies against A β in AD patients, we propose performing high throughput screening of the kinase inhibitor library on mature neurons in parallel to the CRISPR screening. This approach increases the possibility to identify treatments that may affect phosphorylation of Tau Thr231 and, consecutively, the production of A β plaques. Our lab has extensive experience

with automated high throughput screening of compounds libraries with liquid handling systems, and we developed a protocol that minimizes errors and increases throughput and reproducibility of the assays that withstands the rigors of regulatory validation to evaluate the effect of the compounds from the library on the Tau Thr231 levels in mature neurons.

The kinase inhibitor library of choice includes approximately 160 carefully chosen selective and non-selective kinase inhibitors as 10 mM stock solutions in DMSO. This curated library includes inhibitors of a wide range of lipid, receptor and non-receptor tyrosine, serine/threonine, and dual specificity kinases including those belonging to the ROCK, activin-like kinase (ALK), GSK3, PKC, PDGFR, VEGFR, Src, MAPK, CDK, and PI3K families, among many others. It offers expansive coverage, targeting more than 70 distinct kinases and kinase families, as well as numerous additional kinase isoforms and individual kinases within target families. In the next year of the project we will run the screening on neurons to assess the effect of the kinase's inhibitors on the tau phosphorylation levels estimated by MSD assay. In parallel we will run the same screening focusing on neuron survival as final readout. This assay will allow us to identify kinase inhibitors that affect neuron survival, resulting in false positive for reduction of tau hyperphosphorylation. The results from the two assays will provide hit lead of drugs that can be used in combination with the antibodies against A β in AD patients.

No new collaborations arose from this project. We are actively in the process of preparing materials for a letter of intent for a grant proposal to the Harrington Discovery Institute.

References

1. El-Hayek YH, Wiley RE, Khoury CP, Daya RP, Ballard C, Evans AR, Karran M, Molinuevo JL, Norton M, Atri A: Tip of the Iceberg: Assessing the Global Socioeconomic Costs of Alzheimer's Disease and Related Dementias and Strategic Implications for Stakeholders. *J Alzheimers Dis* 2019, 70:323-341.
2. Selkoe DJ, Hardy J: The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Mol Med* 2016, 8:595-608.
3. van Dyck CH: Anti-Amyloid-beta Monoclonal Antibodies for Alzheimer's Disease: Pitfalls and Promise. *Biol Psychiatry* 2018, 83:311-319.
4. Tolar M, Abushakra S, Hey JA, Porsteinsson A, Sabbagh M: Aducanumab, gantenerumab, BAN2401, and ALZ-801-the first wave of amyloid-targeting drugs for Alzheimer's disease with potential for near term approval. *Alzheimers Res Ther* 2020, 12:95.
5. Huang LK, Chao SP, Hu CJ: Clinical trials of new drugs for Alzheimer disease. *J Biomed Sci* 2020, 27:18.
6. Ali T, Kim MO: Melatonin ameliorates amyloid beta-induced memory deficits, tau hyperphosphorylation and neurodegeneration via PI3/Akt/GSk3beta pathway in the mouse hippocampus. *J Pineal Res* 2015, 59:47-59.

**UNIVERSITY OF ARIZONA
PROJECT PROGRESS REPORTS**

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Lifestyle/Physical Activity Biomarkers in Brain Aging & Alzheimer's Disease Risk. Gene Alexander, PhD, (PI), David Raichlen, PhD, Alireza Atri, MD, PhD, Thomas G. Beach, MD, PhD, Richard J. Caselli, MD, Yi Su, PhD, Matt Huentelman, PhD, Yann Klimentidis, PhD, Steve Rapcsak, MD, Eric M. Reiman, MD, Ted Trouard, PhD. University of Arizona; University of Southern California; Banner Sun Health Research Institute; Mayo Clinic Arizona; Banner Alzheimer's Institute; Arizona State University; Translational Genomics Research Institute; 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 older adults with differential risk for AD compared to those that engage in typical lower levels of daily activity; and 2) to develop, evaluate, and implement novel methods for processing and analysis of PA and SQ data to identify new lifestyle/behavioral biomarkers for age-related cognitive decline and AD risk. Additionally, we expect this study will provide significant added value by: 1) evaluating novel wearable biomarkers for the NIA Arizona ADRC Biomarker Core, 2) creating the infrastructure, methods, and a unique dataset to support cognitive aging and AD research across Arizona and nationally, 3) exploring how multimodal neuroimaging relates to PA and SQ in older adults; 4) evaluating how PA and SQ relate to fluid and blood spot 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 population of older adults will grow rapidly over the next two decades and it will be important to respond to the associated growth in AD across Arizona and nationally. Whereas APOE ϵ 4 genetic and cerebrovascular health factors increase the risk for AD, engaging in PA can improve cognition in aging and may reduce AD risk, yet the mechanisms underlying these benefits are not well understood. High PA levels are associated with greater brain volume and connectivity. Studies including highly active older adults are needed to identify how PA supports healthy brain aging, while reducing AD risk. SQ is another critically important part of our daily activity that can influence brain aging and AD risk.

Preliminary Data, Experimental Designs, and Methods:

We recently showed that age-related memory concerns were mediated by hippocampal volume in older hypertensive adults (Van Etten et al., *Neurobiol Aging*, 2020). We found that young adult endurance athletes had increased functional connectivity compared to non-athletes, suggesting engagement in high levels of PA can enhance brain function (Raichlen et al., *Front Hum Neurosci*, 2016). We have also shown that different PA measures are associated with preferential brain effects, with larger hippocampal volumes related to more moderate to vigorous exercise and greater cardiorespiratory fitness associated with larger total brain volumes (Raichlen et al., *Brain Imaging Behav*, 2019). In addition, we recently published an article on PA, brain aging, and AD risk in *Scientific American*, which was featured on the issue cover (Raichlen and Alexander, *Scientific American*, 2020).

This project proposes to conduct evaluations by telehealth video calls, mailings, and in-person meetings to administer 24/7 actigraphy and collect health histories, cognitive measures, self-report scales of PA and SQ, neuroimaging, and blood samples. We plan to enroll healthy older adults, 70 - 84 years of age with differing levels of PA engagement. For this proposal, we plan to leverage support from a complementary awarded NIA R56 grant (MPIs: Alexander and Raichlen) to provide MRI scans and blood samples. We will also continue to develop and test

new actigraphy biomarker methods for aging and AD risk for application in our ADRC Biomarker Core. Strengths of this proposal include 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, blood-based biomarkers; outcomes that may lead to interventions for AD risk; AAC collaborations for new external grant proposals; creation of a unique dataset available to Arizona AAC investigators; 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 and function, and blood markers of AD risk. These studies reflect collaborations focused on developing externally funded grant proposals, as part of a multi-disciplinary, collaborative research program, to identify how differing levels of PA and SQ impact brain aging and preclinical AD. We believe the proposed research has the potential to provide unique and 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 proposals for external NIH funding, as well as further support our ADRC Biomarker Core. Specifically, this project will provide key data and methods to support planned and pending grant submissions, including a follow up to a currently funded NIA R56 grant (MPIs: Alexander, Raichlen) to support a new NIA R01 submission, a pending NIA proposal (MPIs: Alexander, Raichlen, Klimentidis) studying the relation of sedentary behavior to AD risk, and a new proposal to investigate how engaging in high levels of PA influence the risk of AD.

Year End Progress Summary:

We have made significant progress, with numerous publications and new grant funding in the past year in support of our efforts to understand how lifestyle factors and physical activity factors influence brain aging and the risk for AD. In support of this project, we have published articles this year showing how white matter lesion load interacts with genetic risk for AD to influence hippocampal volume in healthy aging (Van Etten et al., *Hippocampus*, 2021). We published articles investigating frontal brain structure and working memory in aging (Evangelista et al., *Cerebral Cortex*, 2021), the effects of white matter lesions on frontal cortex and executive functions in healthy older adults (Boutzoukas et al., *Geroscience*, 2022), improvement in functional brain connectivity after cognitive training in older adults (Hardcastle et al., *Geroscience*, 2022), the neural correlates of a visual attention task in older adults and how functional connectivity is associated with this task (Kraft et al., *Cerebral Cortex*, 2022; Hardcastle et al., *Geroscience*, 2022), and how frontal control networks are related to executive function in healthy aging (Hausman et al., *Geroscience*, 2022).

We have published a genome-wide association study identifying genetic factors associated with the liking of physical activity (Klimentidis et al., *Med Sci Sports Exercise*, 2022). We have shown that exposure to air pollution is an important risk factor for dementia (Parra et al., *Environ Research*, 2022). We also published two articles indicating 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), and these findings were highlighted in several news outlets, including in an article in the *New York Times*. Additionally, we have shown that physical activity is associated with cognitive function in a novel community-based, companion dog model of aging and dementia (Bray et al., submitted).

This AAC project has also directly supported methodological developments and data collection to advance our wearable/digital biomarker efforts for our ongoing \$3.8M NIA grant to supplement our NIA Arizona Alzheimer’s Disease Center (ADC), which established a collaborative Brain Imaging and Fluid Biomarkers Core (Core Leader: Alexander; Co-Investigators: Reiman (ADC PI), Atri, Beach, Chen, Kuo, Trouard, Ryan, Su, Stokes) to provide

enhanced access and expertise for the use of MRI, PET, CSF, and blood biomarkers in combination with measures of PA to foster collaborative AD and aging research across Arizona. Furthermore, these state-of-the-art PA lifestyle measures were included as cutting-edge technology-based biomarkers supporting our new \$5M Biomarker Core (Core-Leader: Alexander; Co-Core Leaders: Atri, Su), as part of our overall \$15.7M NIA Alzheimer's Disease Research Center renewal grant application (ADRC PI: Reiman), which was awarded this year. This new Biomarker Core will provide access, methodological support, analyses, and data to Arizona-wide investigators in the use of neuroimaging and fluid biomarkers to support research in AD and brain aging.

In the past year, we were awarded a new 3.35M NIA R01 (MPIs: Alexander, Raichlen, Klimentidis) to evaluate the effects of sedentary behaviors and other aspects of PA on cognition, brain aging, and the risk for AD. This project is a collaborative effort between Dr. Alexander's lab in Psychology at UA, Dr. Klimentidis in Public Health at UA and Dr. Raichlen at the University of Southern California and will utilize novel network analysis methods and machine learning to investigate how different aspects of low physical activity impact the brain and the risk for AD in older adults.

Additionally in the past year, a new \$4.9M NIA R01 was awarded to evaluate the effects of cerebrovascular disease and extracranial carotid atherosclerosis on the risk for AD (PI: Weinkauf; Co-Investigators: Alexander, Altbach, Nikolich-Zugich, Stokes); and a new \$4.6M NIA R01 grant was awarded this year (MPIs: Grilli, Andrews-Hanna; Co-Investigators: Alexander, Meehl, Huentelman, Rapcsak, Bedrick) to investigate the use of novel smart-phone based technology to track autobiographical thoughts in relation to AD biomarkers and cognitive decline in older adults.

Work from this AAC project also continues to support the development of new methods and complements ongoing studies of PA and sleep quality assessment of 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 older adults, ages 85 to 100+. This complementary effort continues to be underway and reflects ongoing collaborations between the University of Arizona, University of Florida, University of Alabama, and the University of Miami. Initial findings from this work, as part of a graduate student doctoral dissertation has helped to validate the use of the NIH Cognitive Toolbox battery for oldest-old adults (Sims et al., *JINS*, in press) and has identified functional connectivity brain networks associated with cognitive function in this cognitively unimpaired oldest-old cohort (Sims et al., submitted). Additionally, this work has shown that larger and more dentated hippocampal structures are associated with better memory in oldest-old adults (Parpura et al, submitted).

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

An analysis of high-resolution *ex vivo* MRI data from aging macaque brains to estimate white matter microstructure and align histological atlases with MRI images. Carol A. Barnes, PhD, Beth Hutchinson, PhD, Daniel T. Gray, PhD, Laurel Dieckhaus, BS, Ted Trouard, PhD. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aim(s)

- 1) Specific Aim 1 – Postprocess and validate high-resolution *ex vivo* MRI data that was collected over the past year from 12 macaque brains that range from 15 to 32 years of age to create quantitative maps of white matter microstructure.
- 2) Specific Aim 2 – Perform probabilistic tractography analyses on postprocessed DTI data to isolate subcortical white matter tracts for quantitative analyses with respect to age, cognitive, and sensory status.
- 3) Specific Aim 3 – Develop and refine methods for registering *ex vivo* MRI data with histologically-prepared brain sections from the same animals.

Background and Significance

Myelin is a critical component of brain microstructure that surrounds and insulates axons across the brain to allow long-range electrical impulses to transmit efficiently along nerve cells. Numerous MRI studies have shown that normal brain aging results in extensive alterations in myelin structure in multiple brain regions. **While it is clear that white matter microstructure changes with age at multiple levels of analysis, an important open question is what different microstructural changes observable with MRI reflect at cellular levels of analysis.** Insights into this question require quantitative MRI and histochemical analyses to be performed within the same brains so that the two images can be registered to the same space for analysis. The benefits of *ex vivo* MRI imaging, or 'MRI microscopy' of fixed animal brains has recently been appreciated as an important ancillary method to combine with higher-resolution histological studies. Consequently, a quantitative assessment of subcortical white matter condition with aging and an understanding of what cellular-level changes covary with changes in the white matter is timely and an important problem.

Preliminary Data

With the funding obtained from the AAC in the past year, we have achieved our proposed goals of 1) optimizing parameters for the high-resolution scans, 2) demonstrated our ability to visualize small nuclei in the brainstem, and 3) have begun to develop an analysis pipeline that will allow probabilistic tractography to be conducted on these brains. With respect to the optimized parameters for the high-resolution scans we have finalized protocols for anatomical (HRA) imaging, diffusion tensor imaging (DTI), multi-spin echo (MSE), and selective inversion recovery (SIR) imaging and have obtained these scans from all 12 monkeys in this cohort.

Experimental Designs and Methods

MRI template analyses: HRA, DTI, MSE, and SIR images have been collected and customized processing pipelines developed for generating fractional anisotropy (FA), bound pool fraction (BPF), and myelin water fraction (MWF) quantitative maps. Work is ongoing to apply these methods for each of the 12 monkeys in this cohort. Next, the maps and images of these data

sets will be used to create multi-modal whole-brain templates by registering and warping all brain volumes into a common space for the adult and aged monkeys separately.

Analysis of relationships between quantitative MRI and measures of brain function: To facilitate regression analyses between quantitative MRI estimates and estimates of cognitive and sensory function, probabilistic tractography analyses will be performed on each individual monkey to create streamlines that can be used as ROIs to assess the FA, BPF, and MWF of specific white-matter projections.

Brain sectioning and creation of monkey-specific cytoarchitectonic brain atlases: We will serial section two brains from this cohort, one from a young monkey and one from an old monkey. Brains will be cut at 30 microns in the coronal plane and every fourth section will be stained for Nissl to create histologically driven monkey-specific brain atlases. Sections will be used to begin the development of the co-registration of the brain tissue with the high-resolution MRI images. While there is one experiment that has achieved this for two human brains (Wisse et al., 2017), having an N of 6 adult and 6 aged cognitively assessed monkeys will be a unique contribution to the field. To facilitate this process, we will utilize AMIRA software, which uses artificial intelligence and diffeomorphic registration algorithms to assist with registration.

Proposed One-Year and Long-Term Outcomes

- 1) Create monkey-specific quantitative anatomical maps (in MRI space) of white matter anisotropy (DTI maps), macromolecular content (BPF maps), and myelin water fraction (MWF maps) for all 12 animals in this cohort. [Hutchinson and Trouard labs]
- 2) With these data we perform probabilistic tractography analyses to assess the relationship between the above quantitative MRI measures and our estimates of cognitive and sensory function. [Barnes lab]
- 3) Create standardized templates for the adult and aged monkeys separately and perform large-scale voxel-wise comparisons to identify regions in which white matter structure show robust age-associated differences. [Hutchinson and Trouard labs]
- 4) Finalize the methods that will be used to align MRI images to histology images in the two brains that are currently being serial sectioned and Nissl stained. [Barnes Lab]
- 5) Use the data obtained from these aims to prepare an R21 or RO1 in the summer of 2022 to continue to develop quantitative *ex vivo* MRI methodologies to validate the relationship between MRI white matter condition and cellular properties of white matter tissue. Additionally, we will develop an R21 to determine the radiologic-pathologic correspondence between the local neural, vascular and glial responses and quantitative microstructural changes detected by MRI in the young versus aged brains.
- 6) Preliminary results from these experiments will be presented at the Arizona Alzheimer's Consortium meeting in September of 2021 and at the Society for Neuroscience meeting in November of 2021. We will also begin to prepare manuscripts reporting the results of these data during this period.

Year End Progress Summary:

All collected MRI data for this project has been fully processed and two of the brains have been sectioned and stained. We are currently in the analysis phase of this project and anticipate two main lines of research outcomes: 1) tractography-based, histologically verified assessment of the locus coeruleus (LC) projections to the thalamus (central tegmental tract, CTT) and 2) comprehensive assessment of advanced microstructural MRI markers across the whole brain. During the project period, several quantitative methods were optimized for this study including constrained spherical deconvolution (CSD) for fiber orientation distribution (FOD) representation and tractography of the CTT were optimized and verified with established tracts (optic nerve/tract).

Additionally, quantitative susceptibility mapping (QSM) was established for this data set with collaboration and assistance from the Chen lab and a new framework for image importation and data management was established (BIDS) in collaboration with Adam Raikes. In combination with our previously established mapping techniques (i.e. DTI metrics, MAP-MRI metrics, MWF and BPF) our final set of microstructural MRI techniques spans a comprehensive range of tissue environment targets including myelination, macromolecular content, neurite and axonal morphometry among others.

On the group analysis level, we have performed both ROI-based and begun to develop template-based techniques for the MRI data to examine different facets of microstructural changes during aging. Specifically, we have used automated tissue segmentation (atropos) and manual ROI drawing for the hippocampal subfields to extract microstructural values. Tractography of the CTT has been developed and work is ongoing to apply these to all specimens. Specifically, a known test region (optic nerve/chiasm) was first segmented using mrtrix CSD-based tractography (iFOD2) and then a protocol was developed to segment the CTT, which is small and traverses several regions of complex microstructure. For MRI-histology registration, a protocol has been developed and finalized for microscopy. Briefly, Nissl images will be imaged at high resolution 5x using a Leica DMI6000 inverted microscope. These images will be pre-processed in FIJI Bioimage and Adobe photoshop to create stacks of images with appropriate dimensions and imported into a 3D volume to align with MRI data using AMIRA software and a protocol recently developed and tested with in-vivo MRI scans by the Barnes lab.

Initial results from this work have focused on comparative analyses of FA, BPF and MWF metrics in the white matter and hippocampus where an interesting differentiation was found between the two structures.

This work has begun to be presented as abstracts at several conferences during the project period: AAC (2021), Society for Neuroscience (2021), BME Expo (2022) and ISMRM (2021, Power Pitch selection). We have secured FY23 funding to complete the analysis phase of this project and to explore important new directions and are at a point in the project where our initial results can support applications for external funding and our expected analyses will support manuscript preparation.

Challenges The main source of challenge for this study over the past project period has been methods development and troubleshooting with handling the dMRI and QSM data sets. This is expected as these are challenging techniques to implement and it is a credit to the diligence of the students working on these projects that proper quality-assurance analyses were performed and inconsistencies in the data – especially in handling of the diffusion direction information – was identified and addressed. All tractography required this problem to be solved to proceed and CTT tractography is a highly challenging goal such that success in implementing this required considerable extra time and effort.

One-year outcomes

1. (monkey-specific quantitative anatomical maps). All maps have been generated and the project is currently in the analysis phase.
2. (probabilistic tractography analyses). A protocol for CTT tractography was successfully developed and has been implemented in 5/12 samples to date.
3. (standardized templates). Template generation was performed using the FA maps and the resulting transforms were applied to generate templates of other maps (e.g. BPF and MWF). However improved template building is currently underway that uses the full diffusion tensor and will supplant this method moving forward.

4. (Finalize the methods that will be used to align MRI images to histology images). The microscopy and AMIRA importation have been finalized. The alignment protocol will be based on recent work in the Barnes lab using the same Nissl image types with in-vivo MRI in a different cohort.
5. (Funding proposals). We applied for and received additional AAC funding for FY23 and expect to apply for NIH funding within the next year.
6. (Publications and presentations). 4 abstracts have been presented related to this project and we expect to begin manuscript preparation in the next year.

ARIZONA ALZHEIMER'S CONSORTIUM
2021-2022 Scientific Progress Report

Accelerating Diffusion Magnetic Resonance Imaging using Deep Learning. Ali Bilgin, PhD, Ted Trouard, PhD, Craig Weinkauf, MD, PhD, Maria Altbach, PhD. University of Arizona; University of Arizona College of Medicine-Tucson; Arizona Alzheimer's Consortium.

Specific Aims:

The overall aim of this work is to improve the acquisition and analysis of Diffusion Magnetic Resonance Imaging (dMRI) by implementing deep learning (DL) analysis techniques. The specific aims in this project are:

- 1) To complete the development of DL-dMRI by improving the underlying DL techniques and incorporating more advanced diffusion models.
- 2) To evaluate the DL-dMRI approach in different cohorts to measure its impact on subsequent detection/classification tasks.

Background and Significance:

dMRI is a widely used neuroimaging tool. Most neuroimaging studies, including the Alzheimer's Disease Neuroimaging Initiative (ADNI), rely on dMRI to understand WM microstructure and brain connectivity. Improving dMRI acquisition time or, equivalently, the dMRI data quality would have an immediate impact on neuroimaging studies. Furthermore, since the development of DTI, more advanced dMRI protocols, such as multi-shell high angular resolution diffusion imaging (HARDI), high b-value q-Ball imaging and diffusion spectrum imaging (DSI), have been introduced with increasing data acquisition requirements. Acceleration of dMRI data acquisition would enable the use of these advanced dMRI protocols in many neuroimaging studies. Accelerated data acquisition would also reduce problems due to patient motion. Finally, ultrafast protocols enabled by DL-dMRI may enable inclusion of dMRI techniques in routine clinical imaging protocols.

Preliminary Data, Experimental Design and Methods:

Preliminary experiments were conducted using rat dMRI data from Dr. Trouard's lab as well as human dMRI data from the Human Connectome Project (HCP). Preliminary results suggested that DL-based approaches could provide high quality DTI metrics from a small number (4-8) diffusion weighted images (DWIs), which are comparable to DTI metrics obtained using 64-90 DWIs using conventional methods, corresponding to reduction of data acquisition time (approximately) by factors of 10 to 22.

Proposed One-Year and Long-Term Outcomes:

1-year outcomes: We expect multiple publications to come out from our work during the first year. Results obtained in Aim 2 will be incorporated into Dr. Weinkauf's R01 resubmission to enhance the innovation of the grant. Other investigators in Arizona neuroimaging community have also expressed interest in this technology and we anticipate that they will utilize these innovative techniques and incorporate them in their grant submissions.

Long-term: Our preliminary results demonstrate that DL can effectively mine information in noisy dMRI and yield high-fidelity DTI metrics that were previously believed to require far more data (It was believed that DTI requires at least 6 DWIs in the absence of noise; We have shown that we can get relatively high-quality DTI metrics from only 4 noisy DWIs). These results suggest that existing dMRI protocols do not fully exploit the information in acquired DWIs. Extension of DL techniques proposed here for diffusion metric estimation to detection/classification tasks may allow delineation of subtle changes in neuroanatomy, which were not visible to traditional techniques.

Year End Progress Summary:

During the past year, we made progress towards both aims of the project. For Aim 1, we developed a self-supervised DL approach. The DL-dMRI approach we used in our preliminary experiments used fully-supervised DL training. While fully-supervised DL-dMRI enables high quality DTI metrics from accelerated acquisitions, it has several drawbacks: Firstly, the process of training fully-supervised DL techniques requires many datasets, each with a large number of DWIs. Acquisition of these large DWI datasets requires long scans, which are expensive and may be impacted by motion-induced artifacts. To address these shortcomings, we developed a self-supervised DL approach which significantly reduces the training data requirements. Our proposed self-supervised DL-dMRI approach can learn directly from accelerated acquisitions, significantly reducing the required number of datasets with high directional encodings needed for full-supervised training. This DL network pretrained using accelerated acquisitions can then be fine-tuned using a very small number (i.e., one to four) of datasets with high directional encodings. We evaluated this self-supervised approach and compared it with fully-supervised training using data from the HCP. We trained networks using varying number of training subjects as well as DWIs with different number of directional encodings. Our experiments demonstrate that our self-supervised approach is very effective: With only 6-directional encodings, the self-supervised approach can achieve high-quality FA maps that are comparable to reference FA maps obtained using 90 directional encodings. Combining a single 90-directional DWI dataset with fifty 6-directional DWIs for training, the self-supervised approach can match or exceed the performance of the fully-supervised framework, which requires fifty datasets, each with 90-directional DWIs. Preliminary results of this study were presented during the Annual Meeting of the International Society of Magnetic Resonance in Medicine in May 2022. A journal manuscript describing the self-supervised accelerated dMRI approach is under preparation for submission with a target submission date of August 2022. For Aim 1, we also developed a q-space super-resolution approach using DL. The basic premise of this framework is to estimate DWIs corresponding to unacquired diffusion directions and diffusion weightings (b-values) from a small number of acquired DWIs. The software implementation of this approach is complete and we started to run preliminary experiments. Our goal is to submit this work for presentation at the 2023 Annual Meeting of the International Society of Magnetic Resonance in Medicine. A journal submission will follow.

For Aim 2, we are investigating the impact of the accelerated DL-dMRI techniques on subsequent DTI tractography. Using HCP data, we performed DTI tractography on datasets obtained using self-supervised and fully-supervised frameworks developed in Aim 1. Part of these results will be incorporated into the “self-supervised dMRI” journal submission.

At the time of submission of this proposal, our goal was to incorporate some of the results from this work into Dr. Weinkauf’s R01 resubmission to enhance the innovation of the grant. However, Dr. Weinkauf’s R01 was funded without the need of a resubmission. At this time, we are working to develop other extramural funding applications (such as those under the Brain Imaging Initiative from the NIBIB for the development of novel technologies of brain imaging) that will combine the DL-dMRI techniques with other novel quantitative MRI methods developed by our research group.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Network-based statistics (NBS) and graph-based statistics (GBS) for identifying dynamic functional network changes of Alzheimer's disease. Nan-kuei Chen, PhD, Ying-hui Chou, ScD, Chidi Ugonna, MS, Atiyeh Fotoohinasab, MS. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

- 1) To use network-based statistics (NBS) and graph-based statistics (GBS) to identify neuronal network signatures that significantly differ between AD and control groups (from ADNI data)
- 2) To use NBS and GBS to identify network signatures that are significantly correlated with the cognitive performance across the subjects in either AD or control group (from ADNI)
- 3) To use NBS and GBS to identify network signatures that are correlated with disease progression (from the longitudinal data of ADNI)

Background and Significance:

As discussed in the NBS paper authored by Zalesky et al. [1], large-scale neuronal connectivity can be modeled as a network or graph, which not only more accurately captures the brain activity as compared with voxel-wise representation of imaging data but also effectively addresses the challenge of performing multiple comparison correction in conventional voxel-wise fMRI analyses.

NBS has been successfully applied to research of neurological and psychiatric disorders. For example, Hojjati et al. reported the use of NBS (as well as support vector machine) to differentiate MCI from AD using ADNI data [2]. To our knowledge, a systematic evaluation of various graph theory measures, which could be further derived from NBS and GBS analyses remains to be conducted (e.g., in terms of their value in measuring AD-control between-group difference; correlation with cognitive measures; correlation with disease progression). To address this need, here we propose to systematically assess various NBS and GBS derived graph theory measures in capturing AD network signatures using resting-state fMRI data from ADNI.

Preliminary Data, Experimental Design and Methods:

First, our lab has established resting-state fMRI processing pipelines, with which we will be able to convert the resting-state fMRI data from ADNI studies to connectivity-matrix format suitable for the proposed NBS and GBS computation. Second, our PhD student Atiyeh Fotoohinasab has started implementing fMRI-specific GBS procedures, built upon a series of graph theory algorithms that she has developed and published [3-5]. Third, we have recently implemented NBS procedures and applied them to resting-state fMRI data previously obtained from 28 Parkinson's patients and 30 healthy controls. These procedures should be readily applicable to resting-state fMRI data obtained from ADNI studies. Specifically, with NBS we are able to identify inter-connected network nodes with their connectivity strength negatively correlated with the disease duration, across 28 patients of two disease subtypes (tremor; dyskinesia).

Proposed One-Year and Long-Term Outcomes:

First, the software platforms for converting ADNI resting-state fMRI data to network-based and graph-based measures will be completed. Second, using the established procedures we will identify network properties and graph signatures that 1) differentiate AD from controls, 2) are significantly correlated with cognitive performance, and 3) are correlated with AD progression.

Third, we plan to submit a new NIH R01 grant proposal using the preliminary data produced in this project.

Year End Progress Summary:

First, we successfully developed a series of software platforms to convert ADNI resting-state fMRI data to network-based and graph-based measures. During this effort, we use R-language to build a query interface to more efficiently search and identify appropriate images from the downloaded ADNI fMRI data (using our targeted criteria). The built R-based interface is expected to benefit other neuroimaging researchers who plan to examine any of the existing ADNI data sets. We have also built FSL-based pipelines and matlab programs, which are capable of 1) converting voxel-wise fMRI signals to connectivity matrix (for each of the participants), and 2) identifying network-based and graph-based measures from the converted connectivity matrix for each participant.

Second, with an initial success of identifying network-based and graph-based measures between healthy controls and AD subjects, we are now in the process of characterizing the graph-based measures that demonstrate the most significant difference between two subject groups. The findings will be used as preliminary data for our submission of a new NIH proposal, which is currently being planned.

Third, we have also expanded our network-based and graph-based fMRI analysis pipelines to examine dynamic changes of two different time scales: 1) across different time segments within a single fMRI scan session, and 2) across longitudinal scan time points. The new data obtained from this dynamic analysis are expected to further enhance the level of innovation of our planned NIH grant proposal.

References:

1. Zalesky A, Fornito A, Bullmore ET. Network-based statistic: identifying differences in brain networks. *Neuroimage*. 2010 Dec;53(4):1197-207. doi: 10.1016/j.neuroimage.2010.06.041. Epub 2010 Jun 25. PMID: 20600983.
2. Hojjati SH, Ebrahimzadeh A, Khazaei A, Babajani-Feremi A; Alzheimer's Disease Neuroimaging Initiative. Predicting conversion from MCI to AD using resting-state fMRI, graph theoretical approach and SVM. *J Neurosci Methods*. 2017 Apr 15;282:69-80. doi: 10.1016/j.jneumeth.2017.03.006. Epub 2017 Mar 9. PMID: 28286064.
3. Fotoohinasab A, Hocking T, Afghah F. A greedy graph search algorithm based on changepoint analysis for automatic QRS complex detection. *Comput Biol Med*. 2021 Mar;130:104208. doi: 10.1016/j.compbiomed.2021.104208. Epub 2021 Jan 6. PMID: 33484946; PMCID: PMC8026760.
4. Fotoohinasab A, Hocking T, Afghah F. A Graph-constrained Changepoint Detection Approach for ECG Segmentation. *Annu Int Conf IEEE Eng Med Biol Soc*. 2020 Jul;2020:332-336. doi: 10.1109/EMBC44109.2020.9175333. PMID: 33017996; PMCID: PMC7584386.
5. Mousavi S, Fotoohinasab A, Afghah F. Single-modal and multi-modal false arrhythmia alarm reduction using attention-based convolutional and recurrent neural networks. *PLoS One*. 2020 Jan 10;15(1):e0226990. doi: 10.1371/journal.pone.0226990. PMID: 31923226; PMCID: PMC6953791.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Feasibility Study for the Mild Cognitive Impairment with Accelerated Transcranial Magnetic Stimulation. Ying-hui Chou, Sc.D. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

- 5) Specific Aim 1: Determine the efficacy of the accelerated rTMS on memory performance compared to sham treatment
- 6) Specific Aim 2: Evaluate the efficacy of the accelerated rTMS on brain function compared to sham treatment

Background and Significance:

Individuals with amnesic MCI (aMCI) convert to AD at a rate of approximately 10-34% annually. For this reason, aMCI represents a clinical population with an urgent need for therapies capable of both alleviating symptoms and modifying disease trajectory to reduce progression to AD. rTMS is a non-invasive brain stimulation technique that has emerged as a promising therapy for MCI and AD, yet surprisingly little effort has been undertaken to optimize the application of rTMS for these populations.

Accelerated rTMS is a novel rTMS paradigm that was recently developed to consolidate the conventional 2-to-4-week treatment into 2 to 5 days (Holtzheimer, McDonald et al. 2010, Desmyter, Duprat et al. 2014). It has been successfully applied to patients with treatment-resistant depression (Holtzheimer, McDonald et al. 2010, Baeken, Vanderhasselt et al. 2013, Desmyter, Duprat et al. 2014, Baeken 2018, Williams, Sudheimer et al. 2018, Rachid 2019, Sonmez, Camsari et al. 2019). Findings from these studies reveal that the accelerated rTMS procedure is safe, feasible, and capable of producing rapid anti-depressant effects for patients with treatment-resistant depression (Rachid 2019, Sonmez, Camsari et al. 2019). The positive behavioral outcomes within these accelerated rTMS trials were also found to be associated with stronger functional connectivity profiles and enhanced structural integrity of networks associated with the stimulation site (Baeken, Marinazzo et al. 2014, Baeken, Duprat et al. 2017, Baeken, Lefaucheur et al. 2017, Caeyenberghs, Duprat et al. 2019). This novel rTMS paradigm has great therapeutic potential for improving memory function in individuals with aMCI. In this project, we will use theta burst stimulation (TBS), a form of brain stimulation that more closely mimics the natural rhythms of activity in the neurons of the hippocampus (Larson and Lynch 1988, Capocchi, Zampolini et al. 1992, Vanderklish, Saido et al. 1995, Larson and Munkacsy 2015), to stimulate the memory network and evaluate the efficacy of accelerated TBS (aTBS) in individuals with aMCI. Building on the findings of our meta-analysis (Chou, Ton That et al. 2020) and previous studies of accelerated TBS (Desmyter, Duprat et al. 2016, Duprat, Desmyter et al. 2016, Baeken, Duprat et al. 2017, Williams, Sudheimer et al. 2018, Caeyenberghs, Duprat et al. 2019), we hypothesize that aTBS protocol will enhance memory performance and brain function in individuals with aMCI. This project represents a potential step-forward in the development of a clinically feasible non-invasive brain stimulation therapy for individuals with MCI and AD.

Preliminary Data, Experimental Design and Methods:

Our preliminary data from 9 individuals with MCI revealed significant improvement of memory function after single TBS session of TBS, $F = 4.47$, $p = 0.03$. The effect of TBS was also significant on resting-state functional connectivity measures along the hippocampal white matter pathway ($p < 0.05$). Furthermore, individuals with a greater increase in functional connectivity between TBS

stimulation site and subfields of the hippocampus (left CA1 and left hippocampal fissure) showed a larger improvement of memory function ($r = 0.51 - 0.68$, $p < 0.05$).

Aim 1: Determine the efficacy and lasting effects of accelerated TBS on memory performance

Design: Twenty-four individuals with aMCI will be enrolled in this double-blind, randomized, sham-controlled study. Participants will be randomly assigned into one of the two TBS groups: accelerated TBS (aTBS) and sham TBS. The aTBS protocol includes excitatory TBS applied over a superficial node (e.g., parietal lobe) of the memory network. Participants in the sham TBS group will undergo a procedure identical to the aTBS except that a sham TBS coil specifically designed for blinded clinical trials will be used. Outcome measures assessing memory functions will be acquired at baseline as well as immediately and 1 month after the final TBS session. We hypothesize that the aTBS protocol has a stronger effect on memory function than the sham TBS.

Aim 2: Evaluate the efficacy and lasting effects of accelerated TBS on brain function

Design: To investigate how brain function is modulated by the aTBS protocol, we will measure resting-state functional connectivity of the memory network (primary outcome measure) during the baseline, as well as immediately and 1 month after the last TBS session in the 24 individuals with aMCI recruited for **Aim 1**. Functional connectivity of other brain networks, structural connectivity, and brain volume will be the secondary and exploratory outcome measures. We predict that 1) aTBS will increase functional connectivity within the memory network compared to the sham TBS; and 2) alterations in functional connectivity will be associated with changes in memory function in response to the aTBS intervention.

Proposed One-Year and Long-Term Outcomes:

We plan to enroll 12 participants with aMCI this year and additional 12 participants next year. For the long-term outcomes, we submitted an R01 proposing this idea of aTBS. Unfortunately, it was not funded. The major comment from the reviewers is the lack of preliminary data of aTBS effects on memory performance and brain function in aMCI. The data we will acquire carrying out this pilot project will prepare us to resubmit the R01 grant in 2023. The goal of the R01 will be to conduct a large-scale clinical trial to systematically examine aTBS effects and model dose-response TBS effects in aMCI. Our proposal directly targets a major barrier to the clinical feasibility of noninvasive brain stimulation and will likely increase treatment adherence, which is of relevance for patients with cognitive dysfunction. Linear models will be fit to the change scores of memory performance and functional connectivity of the memory network. Correlations between changes in functional connectivity and changes in memory performance will be estimated using the Pearson product moment correlation coefficient.

Year End Progress Summary:

Based on the findings of pilot research projects supported by the Arizona Alzheimer's Consortium (AAC), we are awarded \$409,171 from the NIH/NIA to develop accelerated rTMS treatment for individuals with aMCI (R21AG077153-01). We are very grateful for the support from the AAC! Currently, data from 13 participants with MCI were analyzed. Ten sessions of excitatory rTMS decreased hippocampal functional connectivity. The decrease in hippocampal functional connectivity was significantly associated with enhancement of face-name associative memory performance (i.e., increased d1' score and decreased false-alarm score). We are preparing a manuscript to be submitted to *Brain Stimulation* for publication.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Investigation of age-associated changes in neural coordination and plasticity using advanced high-density neural-ensemble recording technologies. Stephen L. Cowen, PhD, Carol A. Barnes, PhD. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

Millisecond-level coordination between neurons is required for effective neural communication and plasticity. Evidence suggests that such coordination is disrupted in normal aging and age-associated disorders such as Alzheimer's disease and Parkinson's disease. Simultaneous measurement of ensembles of neurons is required for the real-time assessment of neural coordination. Traditional neural recording approaches using wire tetrodes or silicon arrays only resolve < 50 neurons during a typical recording session which significantly limits interpretation and analysis. Recent advances in neural recording technology have led to the development of the Neuropixels system, a recording system that allows measurement from > 2000 electrode sites and > 1000 neurons per recording session in awake and behaving animals¹. This order-of-magnitude improvement is important as it allows for robust assessment of interactions between neurons and brain regions, and how such interactions are affected by age and disease.

The **working hypothesis** guiding our proposal is that inter-region communication between the hippocampus and prefrontal cortex is disrupted in aging, and that this disruption will be most apparent during memory recall and periods of slow-wave sleep associated with memory consolidation. The hippocampus and prefrontal cortex are critical for memory storage and retrieval and interactions between these regions support planning, working memory, and memory consolidation. There is also considerable evidence that these two regions are particularly impacted by aging and Alzheimer's disease.

Broadly, the **hypotheses** guiding this proposal are 1) that neural coordination between the hippocampus and the prefrontal cortex will increase during memory recall and planning, 2) that coordination between prefrontal and hippocampal neurons will increase during slow-wave sleep following a learning experience, and that this increase will correlate with measures of memory recall on the following behavioral testing day, and 3) that correlated activity between task-active neurons in all of these conditions will be disrupted in aged rats. A future goal is to extend these hypotheses and experiments the study of how neural coordination and memory consolidation is affected by Alzheimer's disease.

Our **approach** is, for the first time, to use the Neuropixels system to collect large ensemble data from hippocampal subregions (CA3, CA2, and CA1) and prefrontal subregions (anterior cingulate, prelimbic, and infralimbic) in young and aged rats during learning and sleep. Data will be acquired from 2 young and 2 old rats implanted with Neuropixels arrays while animals sleep and while they perform an associative-learning behavior.

Background and Significance:

Normal aging and Alzheimer's disease is associated with significant changes in the physiology and function of the hippocampus and prefrontal cortex. Interactions between these two structures are critical for memory recall, planning, and sleep-associated memory consolidation. It has been hypothesized that deficits in the communication between individual prefrontal and hippocampal neurons is affected by aging, and that these deficits contribute to age-associated decline in memory recall, memory consolidation, and executive function. This hypothesis has not been explicitly examined due to the formidable challenges involved in acquiring sufficiently large populations of neurons, simultaneously, in both regions to allow for robust evaluation of neural coordination. Recent advances in neural recording technology have led to the development of the Neuropixels system, a recording system that allows measurement from > 2000 electrode sites

and > 1000 neurons per recording session in awake and behaving animals. This order-of-magnitude improvement is important as it will allow far more robust assessment of how coordination between neurons and between brain regions is affected by age and disease. To illustrate, while it is known that aging is associated with reduced millisecond-level precision in neural activity in the CA1 subregion of the hippocampus during slow-wave sleep, how such changes affect interactions between neurons and between brain regions is not understood given the low cell yields from traditional technologies.

Preliminary Data, Experimental Design and Methods:

Our group has decades of experience using high-density neural recording methodologies in anesthetized and behaving rats. This experience directly benefitted the implementation of the Neuropixels system as described in the funded proposal. Prior to funding, no laboratory at the University of Arizona had a Neuropixels system.

Proposed One-Year and Long-Term Outcomes:

One-year outcomes: Acquire simultaneous measures of neural activity from >1000 neurons from 2 young and 2 old rats. Data will be acquired from the hippocampus and prefrontal cortex during an associative memory paradigm and during sleep for the analysis of neural activity associated with memory consolidation during sleep. These preliminary data will form the basis of an NIA R01 proposal that we plan to submit in Spring 2022.

Long-term outcomes: The acquisition of an R01 will allow us to examine in detail the changes in hippocampal-prefrontal network dynamics that result from normative aging as well as in a rat model of Alzheimer's disease. Furthermore, the Neuropixels system has been recently refined to allow for long-term (many months) tracking of the same set of neurons. This advance would, for example, allow within-animal assessment of neural activity through the course of disease progression. Finally, our group also has experience combining neural ensemble measurement technologies with technologies used for measuring dopamine release in the brain (fast-scan cyclic voltammetry)⁵. Thus, another long-term goal is to determine how normative aging and Alzheimer's disease alters the responsiveness of neural ensembles to dopamine release.

Year End Progress Summary:

During the 07/01/21 to 06/30/22 funding period we accomplished the following objectives:

Acquiring and Setting Up Neuropixels Hardware and Software:

- We navigated severe COVID-associated supply chain problems and UA purchasing issues and eventually acquired a complete Neuropixels system by February 2022, ~5 months after initiating the order with UA purchasing. Despite the delays, we were able to get this system up and running within one month and started acquiring data in March.
- The entire system was integrated into a mobile cart, allowing it to be used in the surgery room and rooms dedicated to recording from behaving animals.
- We wrote our own custom software and modified the hardware so that the Neuropixels system could be integrated into our recording and data post-processing pipeline.
- Students and PIs learned how to use the Neuropixels-specific Python and Matlab software for analyzing single-unit activity (Kilosort and Phy).

Data Collection, Analysis, and Grant and Presentation Submissions:

- High-density neural ensemble recordings were acquired from 6 anesthetized rats (5 young, and 1 old 24 mo.) and one mouse (for optogenetic recording). From 100-200 simultaneously recorded neurons were acquired per rat/mouse, and >1000 neurons across animals. As indicated in the proposal, this was an order-of-magnitude increase in the number of recorded neurons per animal. We are extremely pleased with these results as they show a path towards

a deep systems-level analysis of neural activity involved in memory formation and the impact of Alzheimer's disease and aging on these processes.

- In collaboration with Dr. Philipp Gutruf (UA Biomedical Engineering), we used the Neuropixels system to acquire definitive evidence that transcranial delivery of light through skull-mounted LEDs elicited single-unit responses in the cortex and striatum. We observed precise, time-locked action potentials in response to each light pulse. These key preliminary data will allow us to modulate the activities of specific subgroups of cortical and hippocampal neurons so that we can perform causal investigations of the roles of these neurons in memory and decision making and in age-associated cognitive decline.
- Using two Neuropixels probes, we implanted electrodes in both the medial prefrontal cortex and ventral hippocampus and acquired ~150 simultaneously recorded neurons from 1 aged and 1 young rat. This data was used for key preliminary data figures for our (Barnes and Cowen) submitted NIA R01 proposal (submitted in June 2022). This grant will investigate how Alzheimer's disease and aging impact interactions between the ventral hippocampus and medial prefrontal cortex, two regions involved in decision making and memory formation.
- Using a Neuropixels probe implanted in the medial prefrontal cortex and an electrical stimulating electrode implanted in the hippocampus, we were able to measure prefrontal neural activity evoked by ventral hippocampus activation. These data are the basis for our submitted Society for Neuroscience abstract (2022, San Diego SFN meeting). These and follow up experiments will be used determine the anatomical extent to which ventral hippocampal activation impacts prefrontal activity. This information will be critical for refining the design of future experiments.

Challenges:

- The receipt of the Neuropixels system was delayed 5 months due to supply chain issues and to unforeseen administrative delays. Even so, we were able to collect key data that was critical for one of the Aims in our submitted NIA R01 proposal (submitted in June 2022).
- One goal was to adapt the Neuropixels to awake and behaving animals. Given the delays in receiving the system, we were not able to complete this Aim. We are pursuing this objective and we will implant animals with prototype chronic probes in August.

Summary of Grant Applications, Collaborations:

Support from the Alzheimer's Consortium strengthened the ongoing collaboration between Dr. Cowen and Dr. Barnes and directly led to a submitted NIA R01 proposal (June 2022). Support also strengthened collaboration with Dr. Philipp Gutruf (UA Bioengineering) and the development of novel technologies for transcranial optogenetic stimulation of targeted neuronal populations. Furthermore, support resulted in a submitted abstract/presentation for the 2022 Society for Neuroscience meeting. Finally, support provided invaluable training opportunities for at least 4 graduate students in the Cowen and Barnes laboratories. This experience with the Neuropixels system will provide these students with valuable and a highly sought-after background with pioneering neural recording technologies.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 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, John Konhilas, PhD, Lee Ryan, PhD, Nancy Sweitzer, MD, PhD. University of Arizona; University of Arizona College of Medicine-Tucson; Sarver Heart Center; Arizona Alzheimer's Consortium.

Specific Aims:

- 4) 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.
- 5) 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.
- 6) Establish if treatment with Ang-(1-7) modifies the absolute levels of plasma Nfl and the change in the values over 12-months.

Background and Significance:

The proposed project will leverage our recent (April 2021) U01 NIA Administrative Supplement to determine if plasma neurofilament light protein (Nfl) might serve as a Prognostic Biomarker in early Vascular Cognitive Impairment and Dementia (VCID) and Alzheimer's Disease Related Dementias (ADRD) in individuals with stage II/IV heart failure (HF). The present study will provide clinical personnel support for a "sub-project" within this parent project that will allow us to obtain preliminary data to evaluate the safety and efficacy of treatment with Ang-(1-7) to improve cognitive function and determine if this treatment is associated with changes in plasma levels of Nfl protein.

Preliminary Data, Experimental Design and Methods:

We currently have in house 3000 10 mg vials of FDA approved Ang-(1-7) and an active IND from the FDA to enroll and treat 30 subjects with 100 micrograms/kg/day for 90 days.

Study Population: In the parent Nfl biomarker study, participants to be evaluated will be from a group of male and female 45 or older adults with chronic, symptomatic HF (NYHA Class II-IV) recruited from the Banner University-Tucson advanced HF clinic (n=30). A concurrent group of 20 adults matched to the HF group for age, sex, and education, with normal neurologic and cardiac function and no history of HF will be recruited. From this parent study, of those that are willing to also participate in a therapeutic study, we will randomly assign 30 subjects to either 100 micrograms/kg/day Ang-(1-7) via subcutaneous injection for 90 days (n=30) or saline placebo (n=10).

General Methodology Description: We will establish a baseline and 12-month longitudinal Nfl values in HF patients at risk for VCID/ADRD and determine the association between absolute levels of Nfl with measures of cognitive function and MRI in patients with symptomatic HF. We will also determine whether baseline levels of Nfl predict change in cognitive function over a 12-month period. Following baseline assessments of cognitive function, MRI and plasma Nfl levels, 30 subjects who have consented to participate in the Ang-(1-7) sub-study and have 1) some level of MCI, and 2) a baseline plasma Nfl level greater than 30 pg/ml (one standard deviation higher than the mean of 22.8 ± 7.8 pg/ml for healthy controls between 50-60 years of age¹³) will be chosen

and randomly assigned to be given either Ang-(1-7) (100 micrograms/kg/day via subcutaneous injection) for 90 days (n=30) or saline placebo (n=10).

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. We have assembled a unique multidisciplinary group of collaborators who are leaders in their fields. To our knowledge we are the only group investigating a potential intervention for this critical aspect of patients with chronic HF at risk for VCID/ADRD.

Our Long-Term outcome is to demonstrate whether plasma NfL exhibits characteristics making 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. There have been numerous delays and setbacks over the last 12 months including significant IRB delays, Banner Health contract delays, COVID resurgence from Dec 2021- February 2022 and subsequent decline in recruitment from the Tucson heart failure clinic, and adding a new clinical trial recruitment site at UA-COM-PHX/Banner and all related IRB and contract approvals needed.

As of July 1, 2022, the following numbers of subjects have been screened for the HF/NfL study.

2,732: total # of subjects prescreened
470: total # of subjects that met the criteria
28: total # of subjects consented
21: total # of subjects enrolled.

All consented subjects have been approached regarding their participation in the Ang-(1-7) treatment protocol for VCID.

- July-November 2021: IRB submission and contract negotiations with Banner Health ongoing.
- December 2021- February 2022: pause in recruitment from Banner-HF clinic due to COVID.
- February – April 2022: Banner Health delay in contract approval due to inter and intra institutional legal affairs delays.
- March 2022- June 2022: Standing up of 2nd clinical recruitment site at UA-COM PHX/Banner PHX.
- As of July 13, 2022, we now have full IRB approval of both sites and Banner contracts approved and have begun recruiting for the Ang-(1-7) arm of the study.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Migration of microstructural MRI techniques to detect Alzheimer's disease related pathology: from post-mortem MRI microscopy to clinically feasible scan protocols. Elizabeth Hutchinson, PhD, Courtney Comrie, BS, Laurel Dieckhaus, BS, Thomas G. Beach, MD, PhD, Theodore Trouard, PhD, Nan-kuei Chen, PhD, Gene Alexander, PhD. University of Arizona; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

The identification of sensitive and specific brain imaging markers is a primary goal for neuroimaging in Alzheimer's disease (AD). The approach our lab has taken to meet this challenge is through MRI microscopy (high resolution mapping of fixed tissue) in human post-mortem brain specimens, which was recently funded by NIA/NIH via the R03 mechanism and preliminary findings suggest that several of the microstructural MRI methods we've used will provide novel contrasts relevant for detection of AD-related pathology. **In anticipation of submitting an NIA/NIH R01 proposal, we will adapt the most promising MRI microscopy techniques from our R03 project for in-vivo human MRI as a demonstration of feasibility.**

Aim 1: To develop and evaluate human MRI scanning protocols that will enable hippocampal mean apparent propagator (MAP)-MRI, multi-spin-echo (MSE) and selective inversion recovery (SIR) *in-vivo*. In order to achieve high-resolution and high-quality microstructural MRI maps of the hippocampus in-vivo, we will collaborate with the Trouard and Chen labs to establish MRI acquisition methods for field of view (FOV) limited, multi-shot, diffusion EPI.

Aim 2: To establish a robust processing pipeline for hippocampal subfield measurements of MAP-MRI metrics, myelin water fraction (MWF) and bound pool fraction (BPF). Our existing post-mortem data processing pipelines for microstructural MRI mapping will be modified and optimized for the human data acquired in the first aim including the addition of motion correction and optimization of distortion corrections and denoising. A streamlined, open-source code to accomplish this will be generated and made available to other researchers.

Background and Significance:

Currently, neuroimaging is recommended for clinical diagnosis and management of AD and the most applied use of MRI is to identify hippocampal atrophy which is effective during later stages, but insufficient for early detection or distinction from comorbid conditions – a consequential and unmet research goal. In recent years, microstructural MRI methods using diffusion and relaxometry techniques have emerged as promising tools for probing alterations of the local micron-scale tissue environment including cellularity, morphology, protein accumulation among other pathology. The most modern set of diffusion MRI (dMRI) and relaxometry MRI (rMRI) tools hold promise for the development of new non-invasive markers to identify and distinguish AD related pathology, but application to human scanning will require careful development of the image acquisition methods, which must balance a demand for high image quality with clinically feasible scan times.

Preliminary Data, Experimental Design and Methods:

Among several initial findings, the MAP-MRI metric of propagator anisotropy (PA) has a distinct spatial pattern from that of the more conventional fractional anisotropy (FA) from DTI. In the hippocampus, FA is modestly reduced in the AD brain compared with control while PA is prominently increased and decreased in different hippocampal subfields of the AD brain. Additionally, the PA map more clearly shows increased cortical values in the AD brain.

The rMRI metrics of BPF and MWF have also been successfully mapped for both specimens, but do not follow the same striking spatial patterns as PA. We expect that rMRI differences (e.g. BPF increases associated with proteinopathy) will require analysis in a larger sample set and that work is ongoing. *The work of this project to date has been presented at the annual UA BME exposition and the poster was awarded first place in the graduate research division.*

Proposed One-Year Outcomes:

1. Submission of an R01 to NIA/NIH (Feb. 2022 or June 2022 deadline) that includes work from these projects as demonstration of feasibility for MAP-MRI, MWF and BPF hippocampal MRI for short in-vivo human scanning.
2. Three optimized pulse sequences for clinical, hippocampal, microstructural MRI – multi-shell diffusion MRI, multi-spin-echo and selective inversion recovery MRI. These scan protocols will be made available to the AD MRI research community with the full support of our team.
3. Established processing pipelines for the generation of high-resolution temporal lobe maps for conventional and MAP-MRI metrics, MWF and BPF mapping. These processing pipelines will be made available to the AD research community.
4. Publications and presentations: The outcomes of this project, potentially together with outcomes from our post-mortem work, will be shared with the broader research community as manuscripts or conference proceedings including at the AAC retreat and annual meeting.

Year End Progress Summary:

In-vivo human MRI was performed for the first time in our lab for this project and we were able to demonstrate hippocampal rMRI and dMRI techniques similar to several our post-mortem MRI methods. Specifically, we accomplished the following research activities:

- We wrote and obtained an IRB protocol for MRI scanning of human subjects. This is not something our lab has ever done before. We wrote recruitment, consenting and other materials and to support the application and study.
- We recruited human subjects for over 20 MRI scanning sessions during the project as part of two phases:

Phase 1: Protocol Development. During this phase of the project, we performed 10 scan sessions to collect dMRI and rMRI scans with the *collaboration of Dr. Chen and Kevin Johnson*. Between scan sessions, the data were processed and improvements and optimizations to the acquisition were made. In addition, we formed a *collaboration with Drs. Maria Altbach and Ali Bilgin* to implement their work-in-progress (WIP) pulse sequences for radial T1 and T2 imaging.

Phase 2: Reproducibility, Image quality and Template generation. During this phase we performed 2 scan sessions for each of 6 participants using the same set of protocols optimized from phase 1. Imaging data were used to generate dMRI and rMRI maps and test-retest reliability studies within subjects is ongoing to determine the reproducibility of our methods in addition to basic image quality analyses. We are also generating a hippocampal template

- We simultaneously engaged the National Alzheimer's Coordinating Center to obtain human MRI scans and corresponding clinical data in order to optimize our processing and analyses pipelines and to explore a basic finding of our post-mortem work related to diffusivity and T2.

Challenges

Time delays were the most significant challenge, especially a longer than anticipated IRB approval due to migration to the electronic format and a lengthy review process. While waiting for approval, we were still able to develop processing pipelines and become more familiar with human MRIs by initiating work using repository data to investigate our post-mortem findings related to diffusivity and T2. We were pleased to finish the acquisition phases of our project, but note that the delays affected our anticipated timelines for publications and grant submissions.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Modulating liquid phase transition of TDP-43 with tau peptides for AD therapeutics. May Khanna, PhD. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

The specific aim of this project is to develop tau peptides as modulators of phase separation for therapeutic development

Background and Significance:

Amyloid plaque and neurofibrillary tangles (NFTs) are two hallmarks of AD. NFTs correlate with clinical symptoms and may include A β , tau, and TDP-43. Patients with mixed TDP-43, A β and tau proteinopathies exhibit more severe AD-type dementia than patients with A β and tau proteinopathies alone. Tau is a microtubule-associated protein that plays a central role in neurofibrillary degeneration in several NDs. Of relevance here, TDP-43 has been linked to tau mRNA splicing and stability, supporting possible modulation of tau function by TDP-43. There is also evidence of cellular co-localization between tau and TDP-43 misfolded proteins, as well as shared pathways and protein interactions facilitating misfolding of proteins. Lastly, hyper-phosphorylated tau dissociates from microtubules to form insoluble aggregates in neuronal degeneration. Unanswered questions include: (i) does TDP-43 physically interact with tau, and (ii) does phosphorylation of tau influence this interaction.

Our overarching hypothesis is that targeting the novel interaction between TDP-43 and tau may modulate tau pathology.

Finding molecules that can modulate these regions and prevent aggregation is of high significance and will be impactful for design of therapeutics for AD.

Preliminary Data, Experimental Design and Methods:

1. TDP-43 co-IPs with Tau. We tested if TDP-43-tau interaction by immunoprecipitation (IP). In immunoprecipitates from mouse brains (3xTg-AD) with TDP-43 antibody, immunoblotting with Tau revealed a consistent band for Tau. While this is not evidence of a direct interaction, it provides evidence for their existence within the same complex.

2. TDP-43 interacts with Tau in the cytoplasm. Using immunohistochemistry, we tested if TDP-43 interacts with Tau in hippocampal neurons from aged 3xTg-AD mice. Phosphorylated Tau (pTau) was found to co-localize with pTDP-43 in the cytoplasm. This is consistent with previous reports of cytoplasmic TDP-43 in the pathological form in neurodegenerative diseases.

3. TDP-43 interacts with full length Tau at nM affinity. To further validate this interaction, we tested, via microscale thermophoresis (MST), the ability of TDP-43 to bind directly the 2N4R isoform of tau, the largest sized human brain tau. We found a robust interaction ***between TDP-43 and tau with a K_d of 387 ± 72 nM.*** The goal of this aim will be to define the binding interface of tau on TDP-43 and to define the specificity of Tau peptides binding to TDP-43.

4. TDP-43 interacts with tau peptides. We designed a tau array with peptides of 11 amino acids overlapping by 5 amino acids along with phosphorylated peptides, linked to AD. The peptides included pTyr, pSer and pThr. There were in total 43 monophospho-peptides, 8 diphospho-peptides, and tri- and tetra- phospho-peptides. We detected an interaction between full length TDP-43 and specific tau peptides and mapped the interaction on tau's structure. One peptide bound with higher affinity when phosphorylated. Abnormal tau phosphorylation and aggregation are pathological characteristics in Alzheimer's disease. We mapped two peptides' binding site using high resolution NMR on TDP-43 and mapped the binding sites near the RRM domain of TDP-43 in adjacent loop regions.

5. Tau peptides can modulate the liquid phase transition. We have obtained liquid droplets of

TDP-43₁₋₂₆₀ in the presence of (UG)₆ RNA. (UG)₆ RNA is the canonical binding sequence of TDP-43 and binds at nanomolar affinity. This is the first evidence of liquid droplet formation for a TDP-43 construct (TDP-43₁₋₂₆₀) containing the N-terminal and RRM domains in the presence of RNA (manuscript in preparation). TDP-43 alone does not form liquid droplets (data not shown). We then tested the effect of two tau peptides (Tau9-IGSTENLKHQP and its phosphorylated form: Tau10-IGpSTENLKHQP) on TDP-43 liquid droplet formation. Liquid droplet formation and aggregation were enhanced by Tau9. In contrast, the phosphorylated Tau10 peptide disrupted TDP-43 liquid droplet formation. This difference may be due to RNA displacement which may alter protein aggregation or disrupt liquid droplet formation. In this subAim, we will test all 18 peptides to define if the mechanism of LLPS formation is through protein aggregation or RNA-displacement.

Hypothesis. Regulating liquid phase separation for TDP-43 with tau peptides will provide a unique target for AD therapeutics.

Research Design for Aim 1a. The goal of this aim will be to define the interface of TDP-43 to tau. Using 2D NMR, we will test the binding of all tau peptides to the three different TDP-43 constructs and map the interface/interaction. We have obtained the HSQC of the three TDP-43 constructs. We will compare the NMR in the absence and presence of peptides and map the binding site. A total of 18 peptides will be used. These peptides that occur in contiguous regions such as the ones between R3 and R4 (Tau1-Tau18 peptides). These peptides were chosen as they bind with greatest affinity (where higher intensity may correlate with binding). Since phosphorylation appears to increase binding of TDP-43, we will also study four additional peptides containing phosphorylation. Next, we will assess the binding affinity of these 18 peptides to TDP-43 (all three constructs and full length) using SPR, MST – techniques routinely used in our laboratory. For these experiments, we will use proteins purified from *E.coli* and mammalian cells, as described earlier. Both non-phosphorylated and phosphorylated peptides can be purchased from Genscript.

Sub-Aim 1b. Defining the effect tau peptides have on liquid-liquid phase separation of TDP-43. There has been an increasing interest in liquid-liquid phase separation (LLPS) of TDP-43 and tau and how LLPS drives pathology. Proteins can form condensates and sequester RNA in membraneless organelles; these are also known as droplet-like structures, or liquid droplets. Prion-like domains and post-translational modifications are typically associated with phase-separation and formation of liquid droplets. We will investigate how TDP-43's interaction with tau will influence LLPS and how peptide tools can modulate liquid droplets. Aggregation of tau was also recently shown to be initiated by LLPS. Droplet-like tau can be formed in neurons and other cells. It is hypothesized that tau mislocalization may occur as it encounters the somato-dendritic compartment with different local environments, and that those local environments can be reconstituted *in vitro*. How TDP-43 interactions with Tau may contribute to mislocalization and cause phase separation is unknown.

Research Design for Aim 1b. We will test the extent to which the other 16 peptides (at a single concentration of 10 μM) modulate liquid-droplet formation of TDP-43₁₋₂₆₀ and the full-length TDP-43 in the presence of (UG)₆ RNA. We will then determine if there is concentration-dependent effect on the 18 tau peptides on TDP-43 liquid droplet formation. Because the phosphorylated Tau10 peptide disrupted TDP-43 liquid droplet formation, we will mutate the phosphorylated serine residue to alanine (inactive) and aspartic acid (constitutively active) and test if liquid droplet formation is facilitated in the alanine form and aggregation is facilitated in the aspartic form. Next, we will test how full-length Tau affects TDP-43 liquid droplet formation using TDP-43₁₋₂₆₀ and the full-length TDP-43 in the presence of (UG)₆ RNA.

Proposed One-Year and Long-Term Outcomes:

We expect to define all the peptides that modulate the interaction of TDP-43 with Tau and with RNA. We expect that this could be the basis for novel therapeutics for a longer-term project.

Year End Progress Summary:

We mapped out the interaction of the two top peptides that were deemed to have significant changes in the liquid phase separation assay of a TDP-43 construct. Tau9 and the phosphorylated equivalent, Tau 10, were the peptides that most significantly impacted liquid phase separation of TDP-43. Other peptides did not have as significant an impact as peptides 9 and 10. Therefore, we measured perturbations by NMR using ¹⁵N-labeled TDP-43 protein and unlabeled Tau 9 and Tau 10 peptide; this allows us to measure the effect on ¹⁵N residues while the unlabeled residues (in this case tau9 and tau10) are silent. We were able to define several amino acids in the RRM domain of TDP-43 that were significantly perturbed. The NMR data shows that T116, H143 and T203 are some of the most impacted residues in the TDP-43. These residues sit on the loop regions of TDP-43 that connect RRM1 to RRM2 domain. We noticed that the phosphorylated peptide, has a greater more statistically significant perturbation of TDP-43 than unphosphorylated tau peptide.

The fact that the phosphorylated peptide shifts residues in the loop region may imply that this peptide can bind in the presence of RNA. We were not able to test perturbation assays in the presence of RNA using NMR as there were too many shifts. This is planned in future experiments. Because abnormal tau phosphorylation and aggregation are pathological characteristics in Alzheimer's disease, we hypothesize that the differences are more pronounced in pathologically relevant peptides and that those peptides may modulate the liquid phase separation of TDP-43 in a pathological manner. We believe this to be an important feature that could be perturbed in the presence of short unphosphorylated peptides. These peptides will be tested for their effect in more relevant cellular models. Most importantly, we will define if the unphosphorylated or phosphorylated peptides are protective; we predict the unphosphorylated peptides will be protective. One seems to drive towards phase separation and one seems to disrupt phase separation. Therefore, with just a change in PTM, we can define which of these phase modulations of TDP-43 are protective. As it stands, it is not clear which feature would be more advantageous for protection and for disease modulation. The next step of testing the peptides in patient-derived iPSCs will be imperative.

We submitted a R01 on this project, it was reviewed and scored, but not a fundable score. We will test the peptides in cells and resubmit. We have initiated a collaboration with Dr. Hilal Lashuel at EPFL who has an excellent program on tau and we will further define the effect of TDP-43 on tau constructs. This data will also be used in the next submission of a R01 grant.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Treatment of language in Alzheimer's Disease (AD): A pilot study of neuromodulation and language therapy informed by measures of neurodynamics. Aneta Kielar, PhD (PI), Pelagie Beeson, PhD, Steven Rapcsak, MD, Julia Fisher, PhD, Priyanka Shah-Basak, PhD. University of Arizona; Banner University Health Center, Neurology; Medical College of Wisconsin; Arizona Alzheimer's Consortium.

Specific Aims:

- 1) Specific Aim 1: To evaluate effectiveness of individualized fMRI-guided tDCS on languagerecovery in individuals with AD-PPA. We hypothesize that 2 weeks of tDCS combined with language therapy will improve language performance compared to sham.
- 2) Specific Aim 2: To employ neuroimaging measures in the assessment of treatment effects.

Background and Significance:

Atypical variants of Alzheimer's Disease (AD) and frontotemporal dementias frequently manifest with Primary Progressive Aphasia (AD-PPA), disorders of language that slowly expand to other cognitive domains (i.e., attention and memory). Currently, no robust interventions (pharmacological or otherwise) can slow or stop the progression of AD-PPA. Although language training ameliorates some linguistic symptoms, effects have been relatively small, short-lived, and have limited generalization. There is a great urgency for development of treatments that would reduce cognitive symptoms and slow or stop degeneration. We propose that interventions that promote adaptive cortical plasticity by modulating excitability in the frontal-parietal brain networks may slow disease progression and improve cognitive symptoms. In this pilot study, we will apply fMRI-guided noninvasive neuromodulation, called Transcranial Direct Current Stimulation (tDCS) to the frontal and parietal brain regions that show language related activation and still are structurally intact. TDCS will be paired with personalized speech-language therapy to promote neuroplasticity in the task related brain circuits.

Preliminary Data, Experimental Design and Methods:

Methods. This is randomized, double-blind, sham-controlled, cross-over trial. Participants diagnosed with AD-PPA were randomized to receive active tDCS+language treatment or sham +language treatment in a cross-over design. Excitatory/anodal tDCS or "sham" was administered alongside speech-language therapy 5 days a week for 2 weeks to individually determined left hemisphere target.

Overall Design. Participants received anodal-tDCS during the first phase (Phase 1) and then were crossed-over to sham-tDCS during the second phase (Phase 2) following a 2-month rest period. They underwent comprehensive behavioral assessment 1-2 weeks before the first treatment session (A1). These measures were repeated at two weeks following the first phase of the experimental treatment sessions (B1), immediately prior to the second phase of experimental treatment (A2: two months after the end of the first phase), at two weeks after the second phase of experimental treatment (B2), and again at two months following the second phase of experimental treatment (C: follow-up). Assessment was carried out by a speech-language pathologist who was not aware of the tDCS condition. The experimenter who scored assessments was also blind to the stimulation type.

Proposed One-Year and Long-Term Outcomes:

Year 1: Over the first 3 months we recruited, assessed and screened participants. During the next 9 months we collected fMRI data, administered tDCS treatment in combination with language

therapy, follow-up assessments, and prepare publication. In the long-term we plan to submit R01 (~\$2.5 million) grant applications to the NIH-NIDCD and NIH-NIA, FA: Non-Invasive Neurostimulation in AD/ADRD. <https://grants.nih.gov/grants/guide/pa-files/PA-19-298.html>; <https://grants.nih.gov/grants/guide/pa-files/PA-20-183.htm>.

Year End Progress Summary:

The proposed study objectives have been met successfully. During the award period from 07/01/21 to 06/30/22 we assembled and trained study team, recruited participants, developed study protocol and administered treatment protocol. From our sources and collaborators at the University of Arizona we recruited 10 participants with AD-PPA. Five out of 10 completed all study phases including follow-up and remaining five will be crossed over to the other treatment type. Retention has been very high, and the trial is intended to continue until early 2023.

The most dramatic improvements were observed on written narratives (accuracy change from 54% to 89%). Marked improvement was observed in production of well-formed, complete sentences. The magnitude of improvement on the overall writing accuracy was greater in the active tDCS compared to sham. The improvement in the use of function words was also greater in the active tDCS relative to sham phase. The gains on narrative measures were maintained at the 2 months follow-up. These results indicate that language intervention combined with tDCS improves trained skills and generalizes to the functional abilities such as writing. During summer and Fall 2022 we will continue data analysis and collection of neuroimaging data.

Currently we are preparing manuscripts for publication and conference presentations. This Fall we are planning to submit R01 grant to the NIH-NIDCD and NIH-NIA, FA: Non-Invasive Neurostimulation in AD/ADRD. <https://grants.nih.gov/grants/guide/pa-files/PA-19-298.html>.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Development of Brain-Derived Neurotrophic Factor Mimetics. Kathleen E. Rodgers, PhD, Kevin J. Gaffney, PhD. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

- 1) Specific Aim 1: Design and synthesize a series of GSB-106 peptide analogs and small molecule mimetics
- 2) Specific Aim 2: Compare the pharmacology of our BDNF-mimicking TrkB agonists developed in *Aim 1* to BDNF in a TrkB activation assay

Background and Significance:

With the repeated failures of anti-A β antibodies and beta-secretase 1 inhibitors, the identification of novel therapeutic targets for Alzheimer's disease (AD) beyond the Amyloid hypothesis is of the utmost importance. Due to their roles in neurogenesis and neuronal survival, and synaptic plasticity, brain-derived neurotrophic factor (BDNF) and its primary receptor tropomyosin receptor kinase B (TrkB) are targets of growing interest.¹ BDNF is a member of the neurotrophin family of dimeric proteins which are central regulators of nervous system development and homeostasis. BDNF binds at low affinity to p75 neurotrophin receptor and high affinity to TrkB.² The link between TrkB-BDNF and AD has been drawn across several studies. Reduced signaling through BDNF's primary receptor TrkB in heterozygous TrkB (TrkB^{+/-}.5xFAD) mice lead to significant memory impairments.³ Additionally, a BDNF V66M polymorphism in patients with high A β load is correlated with an accelerated decline in hippocampal volume and memory.⁴ Finally, peripheral BDNF levels correlate with AD risk as a one standard deviation increase in BDNF lead to a 33% decreased incidence of AD and dementia.⁵

Taken together, the clinical and pre-clinical data on BDNF & TrkB make a compelling case for targeting the BDNF-TrkB pathway to treat AD. Unfortunately, BDNF is unable to pass the blood-brain barrier and, as a dimeric protein, has poor plasma stability ($t_{1/2} < 10$ min) and bioavailability.⁶ As a result, alternative approaches to BDNF are necessary to harness the therapeutic potential of activating TrkB to prevent cognitive decline in patients suffering from AD. To overcome these shortcomings, we are seeking to develop an orally dosable, metabolically stable, brain-penetrant BDNF-mimicking TrkB agonist.

Preliminary Data, Experimental Design and Methods:

Computational Modeling: The neurotrophin-bound crystal structure of TrkB was used as the starting point for modeling.⁹ The Schrodinger computational suite was used to refine this structure to eliminate any crystallographic artifacts. GSB-106 as then docked into this refined structure using the peptide docking functionality in Glide Schrodinger. Molecular dynamics simulations were carried out to further elucidate the GSB-106-bound TrkB structure. The binding confirmation(s) of GSB-106 informed cyclization strategies and peptide library design. Further, the structures of TrkB underwent virtual screening to identify potential compounds capable of binding to GSB-106's binding site using a virtual library of commercially available compounds.

Small Molecules: The small molecules identified during the virtual screen were purchased from their respective vendors.

TrkB Screening: In order to identify compounds that are capable of activating TrkB, compounds were screened in the PathHunter® eXpress TrkB Functional Assay (DiscoverX) at 10 μ M following the manufacture's protocol. In all assays, BDNF and GSB-106 served as positive controls.

Proposed One-Year and Long-Term Outcomes:

Data and findings from this proposed project will be submitted for presentation at relevant scientific conferences and in peer-reviewed manuscripts. In addition, the results were designed set the stage for the further optimization and development of the BDNF-mimicking TrkB agonists developed in this proposal into a treatment for AD. This work was projected to provide the preliminary data necessary to pursue NIH and/or DoD funding and industry and investor support.

Year End Progress Summary:

During the past year, we have screened a number of literature reported BDNF-mimicking TrkB agonists. We tested these purported TrkB agonists in the PathHunter® eXpress TrkB Functional Assay from DiscoverX which is a highly sensitive assay that directly assesses the ability of compounds to induce TrkB dimerization. The dimerization of TrkB the crucial step in the activating effects of BDNF on TrkB. Unfortunately, none of the literature reported BDNF mimetics or TrkB activators had any effect on TrkB activation, including our positive control, GSB-106. After careful evaluation of the literature surrounding identification of these molecules as mimetics of BDNF's actions on TrkB, we determined that the signals were likely due to artifacts in the assays (eg autofluorescence of the molecules themselves causing a signal). When docking experiments were conducted using these molecules, it appears they are too small to fully engage the receptor. We then went on to screen a number of compounds from previous AAC projects. The only compound we identified that had significant effect on TrkB activation, other than our positive control, BDNF, was our small molecule Mas receptor agonist CAP-1902 which is currently advancing toward NIH-funded IND-enabling toxicology studies for the treatment of Alzheimer's disease. The ability of this compound to positively affect AD pathology was initially identified via an AAC-funded grant. As a result, following the disappointing results of the literature TrkB agonists and the effects of CAP-1902 on TrkB activation, we pivoted our focus to understanding the potency and timing of CAP-1902 and related compounds effects on TrkB activation. This will provide additional mechanistic support underlying the mechanism by which CAP-1902 mitigates neurodegenerative outcomes.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Alzheimer's Focused Analysis Position for the Translational Bioimaging Resource.
Andrew Rouse, PhD, Aneta Kielar, PhD, Matthew Grilli, PhD, Steven Rapcsak, MD, Ying-hui Chou, PhD, Craig Weinkauff, PhD, Theodore Trouard, PhD. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

The specific aim of this project is to establish a neuroimaging analysis core at the University of Arizona in Tucson. This will start with one year of half-time support of a neuroimaging scientist that will be available to a wide group of investigators focused on aging and Alzheimer's Disease.

Background and Significance:

Most neuroimaging research in the TBIR focuses on the study of aging and AD. Currently, investigators rely on their own laboratories and personnel to develop their projects and build the necessary analysis methods. This results in duplications of efforts, a lack of expertise, and leaves individual labs vulnerable to loss when funding gaps occur. In addition, the overall lack of MRI development and analysis services makes it difficult for new investigators without a strong background in MRI to use the state-of-the-art imaging facilities in their aging and AD related research. Funding from the AAC will secure a 0.5 FTE staff scientist position that will offer aging and AD related MRI development, image processing, and data analysis to investigators.

Proposed One-Year and Long-Term Outcomes:

The short-term goal for this project is to fund various neuroimaging pilot studies in the field of aging and AD with the intent of helping investigators obtain extramural funding. Pilot studies and outcomes will be tracked by Dr. Rouse. The long-term goal is to develop an RII supported model to maintain this service beyond this 1-year AAC funding and permanently provide ongoing image processing, data analysis, and project development services to the UA neuroimaging community.

Year End Progress Summary:

Dianne Patterson was hired to fill the neuroimaging analysis position enabled by this AAC funding. Dr. Patterson has worked to develop training material, workshops, standard protocols, and software to support AAC related neuroimaging research on campus. Dr. Patterson has consulted directly with 15 laboratories. In addition to the activities listed below, in order to provide up-to-date information in a quickly developing field, Dr. Patterson reads current publications, evaluates new software, and attends multiple virtual training events.

Training

- **D2L** – Dr. Patterson runs a Neuroimaging Workshop thru D2L that provides evolving resources to improve researchers' practical neuroimaging skills. The site provides links to instructional and reference documents, past presentations, and recorded lectures. 196 researchers belong to the site.
- **OpenClass** – Dr. Patterson provides a selection of interactive online multimedia lessons and reviews using the OpenClass software platform (arizona.openclass.ai). Available practicums are implemented in Google Docs or as Google Cloud Shell tutorials depending on their content and goals. The focus of the existing lessons and practicums is two-fold:
 - Foundational skills (e.g., Unix command line, High Performance Computing, Conda, JupyterLab, Data Management, version control with GIT and Datalad).

- Reproducible pipelines that use the Brain Imaging Data Structure standard, and containerization (Docker and Singularity). Specific materials include DICOM to BIDS conversion, data deidentification, quality control, distortion correction, ASL, and JSON lessons.
- The **Neuroimaging Core Documentation site** (neuroimaging-core-docs.readthedocs.io) provides additional web-based documentation that is publicly accessible.
- **Zoom Workshops** – Dr. Patterson has offered 13 live Zoom workshops during this funding period. These workshops were recorded and are available to the neuroimaging community.

HOURS	LAB PI
0.5	Allen
121	Altbach-Weinkauf
8	Beeson
5	Chen
7.5	Edgin-Lovos
25.5	Grilli-Andrews
36	Kielar
0.5	Lai
26.5	Plante
6.5	Rapcsak
15.5	Reiman
14.5	Ryan
18.5	Saranathan
0.5	Stuehm
2.5	Wilson

Consultations

During this funding period Dr. Patterson has provided more than 285 hours of consultation to 15 separate labs. This included meetings, both via zoom and in person, answering questions and resolving issues via email, grant reviews, article revision, custom scripts, data processing, database troubleshooting, subject scanning, helping to develop SOPs for ASL processing, troubleshooting processing problems, and reviewing scan protocols. The following is a list of consultation hours.

Establish standard protocols

In addition to live teaching and providing training materials related to the BIDS standard and other best practices, Dr. Patterson developed and maintains a set of BIDS Singularity containers and associated scripts on the High-Performance Computing Cluster. These shared resources are available to all researchers to facilitate the use of standardized procedures.

Software Development

Together with Thomas Hicks, Dr. Patterson has developed two tools for use in processing data:

- **Intend4** ([https://github.com/hickst/intend4/](https://github.com/hickst/intend4)) facilitates data preparation for distortion correction
- **QMTTools** - Quality Metrics Tools (<https://github.com/hickst/qmtools>) facilitates quality control

In part because of the impact that Dr. Patterson’s activities have had on brain imaging research, the University of Arizona has committed \$115K in FY23 to support the initiation of a Brain Imaging Center in FY23. Dr. Patterson’s support has also played a significant role in the resubmission of an NIH S10 High End Instrumentation grant for a new Siemens 3T Prisma: NIH 1S10OD032166-01A1, 3T MRI scanner for Advanced Brain Imaging, PI:Trouard.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Evaluating Neurofilament Light Protein as a Marker of Neuronal Damage in Older Adult Survivors of SARS-CoV2. Lee Ryan, PhD, Meredith Hay, PhD, Sairam Parthasarathy, MD, John Altin, PhD, Matt Huentelman, PhD. University of Arizona; Translational Genomics Research Institute North; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

Aim 1: To determine how post-recovery cognitive functioning relates to COVID-19 severity in older adults measured by (1) the presence of respiratory symptoms and hospitalization with ARDS and (2) levels of circulating NFL. We predict that more severe COVID-19 will result in poorer cognitive performance, particularly on tasks that are dependent on the hippocampus.

Aim 2: To determine how brain structure and functional integrity, as measured by MRI, relate to COVID-19 severity in older adults measured by (1) the presence of respiratory symptoms and hospitalization with ARDS and (2) circulating levels of NFL. We predict that more severe COVID-19 may result in smaller hippocampal volume, decreased perfusion, decreased integrity of white matter and the blood-brain barrier, and decreased network connectivity in hippocampal networks.

Background and Significance:

According to the Center for Disease Control (CDC), older adults are at higher risk of developing more severe symptoms that require hospitalization due to COVID-19, making them more vulnerable to poorer outcomes following recovery including cognitive impairment and neurological complications (1-3). In particular, older adults who survive acute respiratory distress syndrome (ARDS) experience a high prevalence of cognitive and sleep impairment that interferes with daily functioning (3,4). This may be due to several reasons. First, SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor which is expressed in endothelial cells in the vasculature, lungs, heart, and brain. In the brain, the ACE2 receptor is found in especially high concentrations within the hippocampus, making this structure particularly vulnerable to localized ischemia (5-8). Viral binding to brain vascular endothelium may also result in a compromised blood-brain-barrier (BBB) (9,10). Second, SARS-CoV-2 leads to a surge of systemic inflammation that can damage immune cells and release of proinflammatory cytokines from macrophages and endothelial cells (11-13). High levels of inflammation along with hypoxia due to respiratory dysfunction, especially ARDS, are likely to result in short and long-term cognitive dysfunction that may accelerate pre-existing cognitive deficits (4,14,15).

Our preliminary data suggest that survivors of ARDS secondary to COVID-19 show significant increases in serum neurofilament light protein (NFL), a known biomarker of neuroaxonal injury and neurodegenerative disease, compared to survivors of similar ARDS who were negative for COVID-19 (see Preliminary Data). Levels were highest in COVID-19 patients with neurologic complaints and systemic inflammation, suggesting that NFL is a possible biomarker for disease severity. Third, neuronal injury may be further facilitated by the presence of Alzheimer's Disease (AD) type pathophysiology, some forms of which are known to be present in brain tissue well before the onset of cognitive decline, rendering the brain vulnerable to both amyloid-beta accumulation and cytokine-mediated hippocampal damage. Risk factors for severe COVID-19 overlap with risk factors for AD and related dementias (ADRD), as well as vascular contributions to cognitive impairment and dementia (VCID). How these risk factors interact with COVID-19 infection, post-recovery cognitive status, and brain structure/function is unknown.

Taken together, we hypothesize that older adults who experience severe respiratory symptoms due to COVID-19 infection are more likely to experience cognitive impairment and changes to

brain structure and function following recovery. These changes may be particularly pronounced in measures of hippocampal integrity, and among older adults with increased genetic risk for ADRD.

Preliminary Data, Experimental Design and Methods:

Neurofilament light protein (NFL) is a known marker for axonal degeneration. Our recent study found higher logNFL levels in ICU patients with ARDS due to COVID-19 compared to similar COVID-19 negative ARDS ICU patients ($p=0.01$). NFL levels were higher in COVID-19 ICU patients with neurologic complaints, cardiovascular disease, and measures of systemic inflammation.

For this proposed study, we will recruit 25 older adults ages 55-79. Participants will include 25 individuals who were previously hospitalized for respiratory dysfunction and ARDS due to COVID-19. An additional 25 participants will be recruited who had confirmed COVID-19 infection without hospitalization and without significant respiratory dysfunction. Groups will be matched on demographics including age, education, and other health factors such as cardiovascular disease and diabetes.

Cognitive testing will be administered, including tests of memory (verbal/visual associative memory, recognition, and pattern separation), executive functions (updating/working memory, inhibition, switching), and processing speed (simple and complex). These tests have been previously used in our laboratory and used previously in the literature to increase sensitivity to subtle cognitive changes in aging. Fasting blood samples will be collected for evaluation of NFL levels, inflammation, and immune function, as well as APOE status.

MRI will be obtained including:

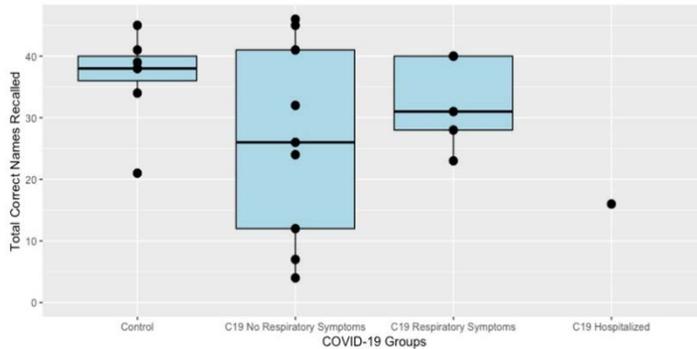
- T1-weighted 3D MPRAGE for gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) volumes.
- T2-weighted 3D FLAIR for white matter hyperintensity volumes.
- High-resolution T2*-weighted imaging for vascular abnormalities and microbleeds assessed from quantitative susceptibility mapping (QSM) reconstruction.
- Diffusion-tensor imaging (DTI): 130 non-colinear directions, b shells (0, 1000, 2000, and 3000 s/mm²), track-specific measures of FA, ADC, axial, and radial in the cingulum bundle and fornix.
- Resting state functional MRI (rs-fMRI) for connectivity measures from EPI (in-plane acceleration factor 2; simultaneous multi-slice factor 3) for established brain networks associated with memory, executive control, frontalparietal and temporal-parietal functions, and sensory-motor functions.
- Cerebral blood flow and BBB permeability will be measured using arterial spin labeling (pCASL) with variable post-labelling delays, and quantitative measurement of myo-inositol as a marker of neuroinflammation using short-echo time MRS.
- High-resolution T2 fast spin echo MRI data (voxel size: 0.4 x 0.4 x 2 mm³) for hippocampal, perirhinal, entorhinal, and parahippocampal volumes of medial temporal lobe subregions.

Proposed One-Year and Long-Term Outcomes:

We are already in the process of recruiting participants to the study, and IRB approval has been obtained. We expect that the study will be completed within the year, and will provide pilot data for an R01 submission in Spring 2022.

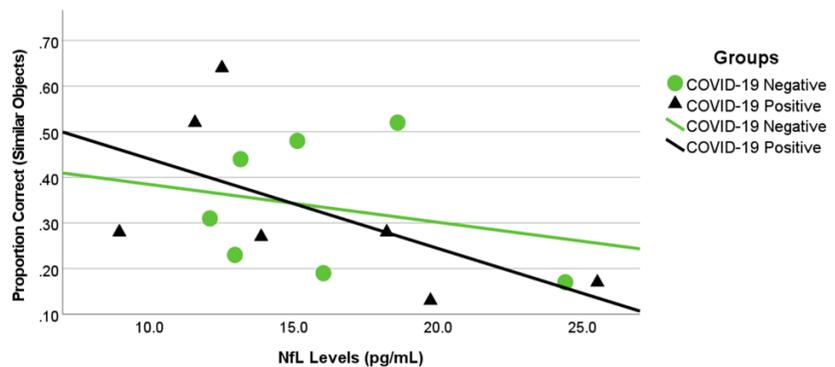
Year End Progress Summary:

We are on track for meeting our target enrollments for the study. We have tested 40+ participants with COVID-19 as well as an additional 20+ controls and others are scheduled for testing and MRI. Preliminary data were presented at the Evelyn F. McKnight Brain Institutes annual conference in spring, 2022, including data from the first 22 participants. We found that all COVID-19+ participants, regardless of respiratory symptom severity, had lower scores on memory tasks compared to age- and education-matched controls.



In addition, NFL levels correlated with performance on a “pattern separation” object discrimination task which is known to be sensitive to hippocampal function. Somewhat surprisingly, NFL levels were correlated with performance for COVID-19 positive and COVID-19 negative individuals, although the correlation was stronger among COVID-19 positive individuals.

These data are consistent with our hypothesis that COVID-19 may result in poorer memory performance, although memory impairment may not be directly related to the severity of respiratory symptoms during COVID infection. However, it should be noted that only two participants in this early group were hospitalized. Since then, we have recruited a larger sample of participants who were previously hospitalized with ADRS, so that we can better assess the relationship between symptom severity, NFL, and cognitive performance. We also found that higher NFL levels were associated with poorer task performance on a hippocampally-mediated test of object discrimination. These data are intriguing, and we currently have additional samples being processed to expand the number of participants in the analyses.



The preliminary results were included in an NRSA submission to NIA by Justin Palmer, a graduate student working on the study. The proposal was scored but not funded, but the feedback on the study was very informative. We plan to submit the expanded results as an R21 or R01 in spring, 2023. The expanded analyses will be submitted to the Society for Cognitive Neuroscience annual conference.

Based on the data collected thus far, it is clear that a number of COVID-19 survivors who report ongoing cognitive problems are younger than age 55, particularly among those individuals who were hospitalized. This year, we will therefore expand the sample to include COVID-19 survivors ages 30-55, as well as demographically matched controls.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Expanding pipelines and data sharing resources for MRI analyses for studies of aging and Alzheimer's disease at the University of Arizona. Lee Ryan, PhD (PI), Theodore Trouard, PhD, Nan-kuei Chen, PhD. University of Arizona; Arizona Alzheimer's Consortium.

Specific Aims:

Specific Aim 1: To expand resources for MRI data sharing and pipelines for standardized state-of-the-art MRI analyses in order to increase access to imaging resources for researchers throughout the Arizona Alzheimer's Consortium. We will create a data management and annotation system to support imaging data, in addition to software pipelines for data harmonization, pre-processing, and analysis of imaging data.

Specific Aim 2: To disseminate information on MRI resources at UA, and to increase interaction with scientists engaged in imaging research and image analysis at other AAC sites across the state.

Specific Aim 3: To submit a T32 training grant for graduate students at UA from multiple disciplines with research interests in studies of brain structure and function utilizing MRI and other imaging modalities.

Background and Significance:

Understanding the variability of cognitive trajectories in normal and pathological aging requires data from large numbers of older adult participants. Many of the most promising approaches to early detection and predicting cognitive decline in otherwise healthy older adults involves MRI measures. Access to state-of-the-art MRI analysis resources is a major barrier for researchers becoming involved in this type of research. Drawing on expertise at UA and our partner institutions within the AAC, we will expand our resources for shared imaging data by creating a data management and annotation system, and expanding our pipelines for standardized state-of-the-art MRI analyses to optimize and streamline MRI methods. A major focus for this year will be the dissemination of this information to researchers at UA and other sites within the AAC, and coordinating with similar efforts underway at ASU. Additionally, given UA's broad expertise related to all aspects of MRI, coupled with major increases in the number of extramurally funded grants over the past few years utilizing MRI, we are in excellent position to write a T32 training grant in the coming year.

Preliminary Data, Experimental Design and Methods:

We will expand our efforts to create a data management and annotation system to support imaging data by configuring a meta-data management and annotation system, integrating the COINS platform (Georgia Tech) with REDCap Cloud, that effectively captures imaging data including data collection, data pre-processing and analyses, minimizes missing data or inaccuracies, supports robust mining, query and analyses of imaging data, and meets the meta-data requirements for various MRI data pre-processing packages and machine-learning processing, as well as large-scale analyses. Our meta-data management system will support both local MRI data (acquired from research laboratories) and decentralized large-scale data (from the public domain), ensuring that publicly available data can be effectively incorporated with new data.

We will also continue our efforts to create software pipelines for data harmonization, pre-processing, and image analysis, implementing software pipelines in Docker (attached to XNAT servers) and Singularity containers (attached to HPC nodes and CyVerse at the University of Arizona). These pipelines will provide quality control and analyses of imaging data leading to quantitative measures of brain morphology, white matter hyperintensities, structural and

functional connectivity, perfusion, diffusion, task-based fMRI, and carotid morphology and blood flow. These software pipelines will be optimized for studies of older adults through machine learning. For example, in order to robustly and automatically segment critical brain structures (e.g., hippocampus) from MR images of older adults, we will optimize machine learning-based segmentation procedures and rigorously validate the developed tools in data obtained from older adults.

In order to disseminate this information to researchers, we will create a user-friendly website with MRI data sharing and analysis resources, including detailed user manuals. Two in-house workshops are planned in the fall and spring semesters, which will demonstrate the use of systems to MRI researchers. Additionally, to coordinate with MRI analysis activities across the AAC, we will hold a day-long meeting at UA in spring, 2022, where researchers at all the AAC sites can share information and discuss future directions.

Finally, we plan to write a T32 graduate training grant that will provide graduate students at UA with exceptional education and research opportunities utilizing MRI research.

Proposed One-Year and Long-Term Outcomes:

1. Establishment of standardized data collection and data management and annotation systems that will support large-scale cross-sectional and longitudinal studies of cognitive aging and risk for Alzheimer's disease.
2. Establish pipelines for MRI analyses using state-of-the-art methods which are optimized for studies of aging.
3. Create a website for neuroimaging research that will provide access to researchers to information regarding imaging resources including detailed user manuals for utilizing data storage systems and analysis pipelines.
4. Submit a T32 training grant focusing on graduate training in MRI research.

Year End Progress Summary:

First, we have established software infrastructures comprising XNAT server (<https://aacazxnat.arizona.edu/>), storage space, embedded image data processing pipelines (in the format of docker containers) and quality control (QC). These components are integrated and made available to neuroimaging researchers who are performing studies supported by Arizona Alzheimer's Consortium. The efforts of developing and maintaining the software infrastructure are led by Chidi Ugonna, under the supervision of Nan-kuei Chen, Ted Trouard, and Lee Ryan.

Second, in collaboration with Dianne Patterson (also with support by AAC), we have organized a series of seminars to extensively discuss various neuroimaging pipelines and made recommendation to various neuroimaging research groups for achieving rigorous and reproducible studies.

Third, in collaboration with Kevin Johnson (an MRI specialist), we have refined and validated a complete set of neurological MRI protocols. The established MRI protocol provide a standard template for ongoing and future neurological MRI studies (supported by AAC and beyond). We have reached to various research groups to help various research groups to incorporate the established procedures.

Fourth, we have initiated new collaboration with Dr. Danny JJ Wang (a Professor at University of Southern California) in implementing advanced arterial spin-labeling (ASL) pulse sequence capable of measuring blood-brain barrier permeability without needing contrast agent. We have identified new application and plan to submit new NIH grant proposals to pursue those studies.

Fifth, we have recently built a new website <https://www.neuroimagingforum.org/> for MRI researchers to exchange knowledge in using advanced MRI protocols. The established website will be used to facilitate a series of MRI workshops (in the fall semester of 2022).

In summary, we have achieved our short term goals, and the outcome of activities are expected to lead to the proposed long-term goals (including submission of T32 and other NIH grant proposals in this coming year).

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Serum matrix effect on amyloid beta detection with FLOWER. Judith Su, PhD, Gene Alexander, PhD, Thomas Beach, MD, PhD. University of Arizona; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

- 1) Specific Aim 1. Compare known spiked concentrations of A β 42 spiked in serum with the recovered concentration using FLOWER.
- 2) Specific Aim 2. Verify the selectivity of the sensing system for A β 42 over other commonly found biomolecules in serum.

Background and Significance:

Sensor assays are typically performed in bodily fluids such as blood and urine to look for biomarkers for disease diagnostics. Of interest is how the matrix (e.g., serum), affects biomarker detection. Here, we quantify serum matrix effects on FLOWER, an ultra-sensitive optical sensing technology developed in our lab.

Preliminary Data, Experimental Design and Methods:

Preliminary data shows detection of A β 42 via FLOWER in HEPES buffer. Next we will examine how a serum matrix affects A β 42 sensitivity and selectivity. To probe these effects, we will investigate the detection of A β 42 spiked in serum using FLOWER. Recombinant human serum albumin (HSA, 6% SigMatrix Serum, Millipore Sigma) will be used for the A β 42 spiked serum experiment. Since the undiluted serum is too viscous and may break the tapered fiber during sample injections, we will prepare the serum with a 1:10 dilution factor (i.e. 10% serum (w/v)). The selectivity of the sensing system for A β 42 compared to other commonly found biomolecules in serum will be verified. In particular, we will compare the binding of A β 40 and Tau352 to A β 42.

Proposed One-Year and Long-Term Outcomes:

Our proposed one-year outcome is to quantify the serum matrix effect for detection of amyloid-beta 42 using FLOWER. Our long-term outcome is to perform protein biomarker detection in serum from patient samples and use this for early detection of AD (as well as other neurodegenerative diseases) before symptoms appear.

Year End Progress Summary:

The sensor's capability to recover the detection signal in bodily fluids (e.g., serum or urine) is essential to clinically relevant applications. To probe these effects, we investigated the detection of A β 42 spiked in serum conditions. To prevent any measurable contaminants typically found in stripped human serum, recombinant human serum albumin (HSA, 6% SigMatrix Serum, Millipore Sigma) was used for the A β 42 spiked serum experiment. Since the undiluted serum is too viscous and may break the tapered fiber during sample injections, we prepared the serum with a 1:10 dilution factor i.e., 10% serum (w/v) condition. Results from spiking different concentrations of A β 42 in simulated serum show that the lipid toroid biosensor is capable of accurate detection in complex media. The recovery rate from each A β 42 spiked concentrations of 10, 100, 1000 pM detected in serum are 58% (coefficient of variation 39%), 141.9% (coefficient of variation 15.1%), and 122% (coefficient of variation 20.8%), respectively.

The proposed long-term outcome of this project is to develop an ultra-sensitive and selective diagnostic and prognostic tool for Alzheimer's Disease (AD). To do this, we are quantifying A β 42 levels in serum and cerebral spinal fluid from cadavers at various stages of AD. One challenge

we have encountered is reliability determining the amount of A β 42 in serum samples. We will address this in the next project period, by quantifying A β 42 using the standard addition method which involves spiking known concentrations of analyte (in this case A β 42) into our patient samples and extrapolating what the 0 concentration point should be which would be the case with no added A β 42.

In addition, one significant challenge we have encountered is the throughput of our experiments. Currently, our throughput if all goes well is one patient sample per day; however, we have ~ 100 samples to quantify. We are working on the instrumentation side to better automate our system in order to improve our throughput as well as experimental reliability. One challenge we have encountered here involves our method of coupling laser light into our sensor. This is important as this is how we interrogate our sample. At the moment, we use a tapered optical fiber to couple light into our system. When we flow patient samples over our toroidal sensor, it can disturb the contact between the optical fiber and our sensor generating unwanted errors in signal. One method we are investigating is implementing a feedback control system for positioning our optical fiber relative to our sensor. This should hopefully minimize this error. In addition, one hindrance towards improved throughput is that as we flow patient samples over our sensor, if the optical fiber position is disturbed and no one is watching the system to re-position the fiber, the experiment effectively ends. This prevents someone from loading the samples and walking away. This degree of automation is one of our ultimate long-term goals. Currently, although biomarkers can be detected in under 30 seconds with FLOWER, experiment time is prolonged as we first need to generate a calibration curve and then flow patient samples over our sensor as well as perform a rinse step in between each sample. Having a fully automated system would decrease the burden on the experiment and would eliminate the need for a trained operator.

As a much longer-term goal, we are working on combining our system with spectroscopic approaches in order to eliminate the need for capture antibodies on the surface of our sensor. This would decrease the complexity and cost of our experiments. In addition, we anticipate that this would lead to higher sensitivity as the addition of antibodies to the surface of our sensor reduces the quality of our sensor. This is because particles (in this case antibodies) attached to the surface of the sensor causes light to scatter out of our system and degrades the quality of our signal.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Imaging and Therapy in Rodent Models of Aging, Alzheimer's Disease and Parkinson's Disease. Theodore Trouard, PhD, Gene Alexander, PhD, Carol Barnes, PhD, Michael Sierks, PhD. University of Arizona; Arizona State University; Arizona Alzheimer's Consortium.

Specific Aims:

1. Complete the analysis of diffusion MRI data from a cohort of 111 rats collected within two NIH R01 grants on cognitive aging and hypertension. Processing and analysis includes constrain spherical deconvolution (CSD) to ascertain white matter microstructure and compare the effects of age and cognition via fixel-based analysis (FBA).
2. Complete experiments in the line 61 mouse model of PD investigating the effect of a novel antibody therapy that targets toxic forms of alpha-synuclein. Antibody therapy is being given with and without prior BBB opening via MRlgFUS.

Background and Significance:

MRI is a valuable and readily translatable tool for assessing brain anatomy, function and structural connectivity in AD and age related dementias. Rodent models of aging and Alzheimer's disease provide unique opportunities to combine in vivo behavioral and imaging studies with detailed post mortem analysis. Through two R01 grants, our research group has carried out high-resolution anatomical and high-directional multi-shell diffusion weighted MRI experiments on multiple cohorts of rats that have undergone detailed behavioral characterization. It is critically important to be able to finish the analysis of this dataset as it will set up multiple labs to publish multiple papers and allow continued research in this area.

In addition to diagnostic imaging, MRI is now being carried out in conjunction with novel therapy that uses ultrasound to transiently permeabilize the blood brain barrier, making it permeable to therapeutics and immunogenic molecules. The technique, referred to as MRI-guided focused ultrasound (MRgFUS) has been carried out in animal models, including non-human primates, and shown to be safe and potentially effective for treatment of neurological disorders [Hynynen, 2008; Downs, 2015]. Because of its safety and promising results in animal models, clinical trials are underway to evaluate the safety and efficacy of FUS-mediated BBB in humans for treating AD [Lipsman, 2018]. The Trouard lab at the University of Arizona has developed the capability for conducting MRgFUS in mice and in a recent publication has demonstrated the technique for delivering various size molecules to the brain in mice [Valdez, 2020]. An ABRC grant has funded research to assess this technique in combination with novel antibody therapy developed by Dr. Sierks. We are currently in the middle of the experiments and the grant expired 3/1/2021. Funds are needed to complete the study, publish the results, and apply for an NIH R01 grant. In addition to the ABRC funding, an NIH/SBIR grant was recently obtained in collaboration with Microvascular Therapeutics Inc. to evaluate novel acoustically active droplets for plaque binding and disruption.

Preliminary Data, Experimental Design and Methods:

Specific Aim 1 will employ ANOVA and ANCOVA analysis of our rat brain dMRI and behavioral data. The effects of Age and Cognitive Status (assessed via memory and working memory tasks) on multiple diffusion metrics, e.g. Mean Diffusivity (MD), fractional anisotropy (FA), Apparent fiber density (AFD) and Fiber density and cross section (FDC), will be determined throughout the entire brain. Specific Aim 2 will complete an ongoing study of PD mice undergoing treatment with antibody and BBB opening. Therapy is given every two weeks (Ab alone, Ab+BBB opening, BBB opening alone) for three months. Behavior tests are carried out every two weeks during this time.

At the end of the study, brain will be perfused, extracted and assessed for the presence of Ab and alphasynuclein.

Proposed One-Year and Long-Term Outcomes:

The completed processing and analysis of dMRI data in the rat model of aging (Specific Aim 1) will allow comparison of neuroanatomical correlations with behavior and help elucidate neuro-correlates of healthy cognitive aging. This should result in **a submitted manuscript**, on changes in brain microstructure with age and its association with cognition. Our MRgFUS methodology for treatment and delivery of therapy in mouse models of PD and AD has already resulted in successful ABRC funding (**ADHS16-00005489**), NIH funding (**R43AG067894-01 with Microvascular therapeutics Inc.**) and an STTR submission (**R41 NS124450-01 with NuvOx Pharmaceuticals**). We expect to submit an additional NIH R01 grant based on this work.

Year End Progress Summary:

Specific Aim 1. The processing of anatomical-MRI and diffusion-MRI has been completed and we are in the process of carrying out the statistical analysis of the results in comparison to rat age and cognition. In addition to the cohort of 111 rats we analyzed for cognition, we have carried out processing and have begun analysis on a second cohort of 70 additional rats involved in experimental hypertension. This addition delayed the analysis of our imaging but puts us in a place to finish up two projects simultaneously. An abstract was presented at the 2021 Society for Neuroscience meeting and two have submitted for the 2022 Society for Neuroscience meeting.

Specific Aim 2. The imaging and therapeutic study in PD mice described in Specific Aim 2 has been completed and brains of all animals have been sent to collaborators at Arizona State University of immunohistochemical evaluation. Results from imaging and behavior have been compiled and the results were shared at the Flinn-ABRC annual meeting.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Understanding increased neurofibrillary tangle accumulation associated with carotid vascular disease. Craig Weinkauf, MD, PhD, Juan Arias, MD, Paulo Pires, PhD, Thomas G. Beach, MD, PhD. University of Arizona; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Specific Aims:

We hypothesize that subjects with ECAD will have increased AD-specific biomarkers as defined by CSF biomarkers compared to matched subjects without ECAD.

Background and Significance:

ECAD prevalence is 9% in men and 7% in women, ages 66 to 93. With the aging population, ECAD is expected to increase greatly in coming decades. ECAD affects the internal carotid artery (ICA), which provides the primary blood supply to the majority of the brain. The vertebral arteries supply the posterior brain directly and are connected via Circle of Willis (COW) collaterals to the anterior circulation. Compared to other cerebral arteries, the unique morphologic structure of the carotid bifurcation induces endothelial dysfunction and atherosclerosis. ECAD is considered clinically relevant when stenosis is $\geq 50\%$ and treatment with antiplatelet agents, statins, and comorbid conditions (diabetes and hypertension) is recommended. CEA or carotid stenting is offered for stroke prevention in select patients. However, cognition and dementia risk is not evaluated or treated despite growing evidence that ECAD contributes to these conditions. This is particularly important in "asymptomatic" patients (ie, no stroke or TIA in previous 6 months) because intervention is not typically offered.

We recently found that ECAD is associated with increased NFT accumulation based on post-mortem brain biopsies (see preliminary data), yet whether this may contribute to AD-specific neurodegeneration vs generalized neurodegenerative patterns is not clear. This is highly relevant because ECAD may be a modifiable risk factor for dementia risk. Our work strongly questions the diagnosis of "asymptomatic" ECAD and aims at changing diagnosis and treatment goals in this patient population particularly in light of growing data (including our own) suggesting that ECAD contributes to cognitive dysfunction. Cognition is a critical outcome to consider, as impairment is associated with medication adherence, disability, dependence, higher healthcare cost, and higher caregiving needs.

Preliminary Data, Experimental Design and Methods:

Our prospective longitudinal clinicopathological study, the Arizona Study of Aging and Neurodegenerative Disorders/Brain and Body Donation Program, records the presence or absence of clinically diagnosed ECAD and does semi-quantitative density estimates of NFT at death. After adjusting for potential confounding factors determined by logistic regression analysis, histopathology density scores were evaluated in individuals with ECAD (n=66) and individuals without ECAD (n=125). We found that the presence of ECAD is associated with a 21% greater NFT burden at death compared to no ECAD ($P=.018$), being significantly higher in the temporal lobe ($P=.05$) and the entorhinal cortex ($P=.02$), an area affected early in AD neurodegeneration. These findings indicate that ECAD is associated with NFT burden in the temporal lobe and entorhinal cortex, key brain regions for the development of AD and non-AD dementias and cognitive dysfunction.

Proposed One-Year and Long-Term Outcomes:

One-year outcomes: Study subject samples will be acquired, and CSF biomarkers will be quantified.

Long-term outcomes: RO1 submission for evaluation of NFT accumulation in subjects with and without ECAD.

Year End Progress Summary:

CSF samples were purchased from Banner Sun Research Institute as proposed. As originally proposed, the core lab that was planning to help perform specific assays under our guidance was no longer able to accommodate this project. As such, a graduate student was hired to work on this project and trained by Dr. Weinkauff to perform Enzyme-linked Immunoabsorbance Assays (ELISAs). New cutting-edge technology equipment was acquired to execute the project, such as the Accuris Platewasher and the Accuris ELISA microplate Reader as well as the needed supplies. In addition to the ELISA kits quoted in the grant application, we acquired kits to test for biomarkers of neuroinflammation including YKL-40, TREM-2, sVCAM-1; a marker of blood-brain barrier breakdown like Platelet-derived growth factor receptor beta (PDGFR B) and Glial Fibrillary Acidic Protein (GFAP), markers associated with hypoperfusion in the central nervous system such as the Vascular Endothelial Growth Factor (VEGF) and the Hypoxia-Inducible Factor (HIF-1). Out of the above-mentioned analytes, we have successfully tested for YKL-40, GFAP, NFL, and sVCAM. We are planning to run the remaining analytes and complete experiments by the end of August. At this point, we expect to perform the statistical analysis to test our hypothesis, and explore additional pathways related to inflammation, hypoxia, and blood-brain barrier integrity. We encountered some unexpected delays specially finalizing the material of transfer agreement between the University of Arizona and Banner Sun Health Research Institute, this took approximately 4 months, and encountered additional delays purchasing supplies and equipment needed to run the experiments due supply chain shortages.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Role of Astrocytic Mitochondria in Brain Metabolism and Neurodegeneration. Fei Yin, PhD, Haiwei Gu, PhD, Francesca Vitali, PhD. University of Arizona; Arizona State University; Arizona Alzheimer's Consortium.

Specific Aims:

- 1) Specific Aim 1. To determine the effect of astrocytic mitochondrial dysfunction on hippocampal transcriptome
- 2) Specific Aim 2. To determine how dysfunctional astrocytic mitochondria reprogram brain metabolic profile
- 3) Specific Aim 3. To determine the effect of astrocytic mitochondria dysfunction on brain synaptic function and neuroinflammation

Background and Significance:

The brain has a bioenergetic system that is more complex than peripheral tissues, largely due to the diverse metabolic phenotypes of different cell types within the organ. Mitochondria are powerhouses of the cell, and their dysfunction has been well-documented as an early event in Alzheimer's disease (AD) and other neurodegenerative diseases. However, previous research has been predominantly focused on neuronal mitochondria, with the pathophysiological role of astrocytic mitochondria poorly understood.

Our recent report (Qi *et al.*, Cell Rep 2021; supported by AAC 2019-2020) demonstrates that astrocytic degradation of fatty acids (FAs) in mitochondria is vital for neuronal metabolic and synaptic function, and ApoE4, the strongest genetic risk factor for sporadic AD, disrupts astrocytic FA degradation within their mitochondria. These results suggest a critical role of astrocytic mitochondria in performing FA degradation, but how this modulates brain lipid homeostasis and contributes to AD-related pathologies is unknown.

Research proposed herein addresses the knowledge gap of astrocytic mitochondria in the brain metabolic system and provides new information on the role of brain lipid metabolism in the etiology of AD and neurodegeneration.

Preliminary Data:

To investigate the role of astrocytic mitochondria in brain metabolism and their potential role as related to lipid homeostasis, we generated an astrocyte-specific mitochondrial dysfunction model by conditionally knocking down the transcription factor A mitochondrial (Tfam) in astrocytes (hereinafter refer to as Tfam^{AKO}). Our initial characterization of the Tfam^{AKO} mice have validated the reduced expression of Tfam in mouse hippocampus and confirmed the conditional depletion in astrocytes. Further, initial behavioral test for novel object recognition (NOR) suggested that compared to wildtype (WT) controls, the Tfam^{AKO} mice have deficits in recognition memory.

Experimental Design and Methods:

Transcriptomic, metabolomic and functional characterizations of the brains of 6-month-old Tfam^{AKO} mouse will be performed as described below. The Cre negative littermates of the Tfam^{AKO} strain will serve as the WT controls.

Aim 1. To determine the effect of astrocytic mitochondrial dysfunction on hippocampal transcriptome and to identify affected pathways. In this aim, polyadenylated RNA will be extracted from the hippocampi of the Tfam^{AKO} and control mice. mRNAs will then be sequenced and aligned against mouse cDNA transcripts using salmon. Tximport and DESeq2 will be used to normalize read counts. Differentially expressed genes (DEGs) will be identified. Subsequent bioinformatic analysis will focus on specific genesets (e.g., Gene Ontology, KEGG, REACTOME and cell-

specific RNA-seq database), particularly those relevant to metabolic, synaptic and cognitive functions.

Aim 2. To determine how dysfunctional astrocytic mitochondria reprogram brain metabolic profile. In this aim, pathway-specific targeted detection of more than 400 metabolites in the hippocampi of the *Tfam*^{AKO} and control mice will be performed by LC-MS/MS in collaboration with Dr. Haiwei Gu's group. Global lipidomics profile will be determined by LC-MS for ~400 lipid compounds. Metabolome data will be pre-processed, statistically analyzed, and visualized using MetaboAnalystR. Analysis will focus on the preference, dependence and capacity of metabolic pathways including glycolysis, pentose phosphate pathway, TCA cycle, ketogenesis / ketolysis, fatty acid synthesis and degradation, and cholesterol metabolism. Metabolomics data will also be connected to RNA-seq data of genes regulating metabolic reactions obtained from Aim 1.

Aim 3. To determine the effect of astrocytic mitochondria dysfunction on brain synaptic function and neuroinflammation. For synaptic assessment, coronal 350 μ m thick hippocampal slices with surrounding cortical tissue will be used for long-term potentiation (LTP) and input/output (I/O) analysis using multi-electrode array (MED64). Further, brain sections will be stained for synaptic marker PSD95 and dendritic marker MAP2. Flow cytometry will be used to quantify microglial activation with activation markers MHC-II and CD74. Pro- and anti-inflammatory cytokines in brain tissue will be measured by the cytokine multiplex array (Meso Scale Discovery).

Proposed One-Year and Long-Term Outcomes:

Upon completion of the proposed studies, we expect to further the understanding of the role of astrocyte in brain energy metabolism as it relates to neurodegeneration and AD. We expect to explore whether and how mitochondrial dysfunction in astrocytes contribute to the bioenergetic decline seen in the aging- and AD brains. Results obtained from this study will be used to seek external funding from the National Institute on Aging or private agencies to support our hypothesis that mitochondria dysfunction in astrocytes contributes to the early pathogenesis of Alzheimer's by disturbing lipid homeostasis in the brain.

Year End Progress Summary:

Astrocytic Mitochondrial Dysfunction Causes Cognitive Impairment and Neurodegeneration

Tfam regulates the replication and transcription of mitochondrial DNA (mtDNA) that encodes essential subunits of oxidative phosphorylation (OxPhos). Upon *Tfam* depletion, mtDNA copy numbers and mtDNA-encoded transcripts of complexes I, III, IV and V were significantly reduced in 6-month-old mouse brains. Functionally, astrocytes isolated from *Tfam*^{AKO} brains showed reduced respiratory capacity, confirming an astrocyte specific OxPhos deficit.

Consistent with our preliminary data suggesting a cognitive impairment, astrocytic OxPhos deficit (*Tfam*^{AKO}) resulted in a decline in hippocampal LTP, the principal mechanism underlying long-term memory and learning. Compared to WT controls, hippocampal slices of 6-month *Tfam*^{AKO} mice failed to sustain synaptic activity following high frequency stimulation. *Tfam*^{AKO}-induced cognitive and synaptic deficits were also accompanied by compromised dendrite complexity as indicated by MAP-2 immunostaining, as well as reduced synaptic density as indicated by the immunostaining for post-synaptic marker PSD-95 in the hippocampus. Further, hippocampal transcriptomic analysis confirmed synaptic deficits in *Tfam*^{AKO} brains. Heatmap of the top differentially expressed genes (DEGs) and principal component analysis (PCA) revealed a dramatic distinction between the transcriptome of WT and *Tfam*^{AKO} mouse hippocampus, with 3,438 gene upregulated and 3,016 genes downregulated in the *Tfam*^{AKO} group (FDR-corrected $p < 0.05$). Key synaptic genes were downregulated in the *Tfam*^{AKO} group, and pathway enrichment analysis revealed that the top 10 Gene Ontology (GO) Biological Processes underrepresented in *Tfam*^{AKO} hippocampi were all related to synaptic function and neurotransmission. Moreover,

Tfam^{AKO} mice were also characterized by neuroinflammation manifested as reactive astrogliosis, microglial activation, and elevated levels of pro-inflammatory cytokines in the hippocampus.

Together, these data suggest that a functional mitochondrial OxPhos machinery in astrocytes is essential for brain function, and its loss induces neurodegeneration characterized by memory impairment, disrupted synaptic transmission, and neuroinflammation that recapitulate critical features of AD.

Astrocytic OxPhos Is Essential in Maintaining Brain Lipid Homeostasis

Abundant clinical evidence has demonstrated disrupted lipid homeostasis –including the accumulation of lipid droplets (LDs)– in early stages of AD, but how lipid dyshomeostasis and LD accumulation emerge in the degenerating brain remain elusive. Utilizing the Tfam^{AKO} mice, we discovered that mitochondrial OxPhos is indispensable for the degradation of FA and protects the brain from lipotoxicity. Tfam^{AKO} induced accumulations of free FAs and neutral lipids including triacylglycerol and cholesteryl esters, which were paralleled with abundant astrocyte-located LDs in the hippocampus, and to a lesser extent, the cortex. Astrocytic mitochondrion-initiated perturbation to brain lipid homeostasis was further characterized by a targeted lipidomic panel, with 101 of the 153 detected lipid species differentially expressed in Tfam^{AKO} brains relative to WT controls, including increased levels of ceramide species and decreased levels of phosphatidylserine and phosphatidylinositol species. These findings suggest that although astrocytic mitochondria are functionally less active (lower OxPhos activity) and bioenergetically less significant (less ATP production) than their neuronal counterparts, a modest level of OxPhos activity is required for the degradation of FA and the homeostasis of all lipid classes in the brain. These data provide new insights into the unique role of astrocytes in maintaining brain lipid homeostasis, and potentially, in protecting the brain from lipid-implicating neurodegenerative disorders including AD.

Partially based on findings from these investigations, a NIH R01 application was submitted in June 2022 to explore disrupted FA degradation as a mechanism of lipid dyshomeostasis in early AD. The application is currently under review.

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Cognitive Effects of Carotid Disease and Carotid Intervention. Wei Zhou, MD, Ted Trouard, PhD, Ying-hui Chou, PhD, Salil Soman, MD, Greg Zaharchuk, PhD, Chiu-Hsieh Hsu, PhD, Thomas Hastukami, MD, PhD. University of Arizona; Surgical Services Southern Arizona VA Health Care System; Beth Israel Deaconess Medical Center, Harvard Medical School; Stanford University; University of Washington; Arizona Alzheimer's Consortium.

Specific Aims:

- 1) Identify the characteristics of SBIs that affect cognition
- 2) Determine the impact of CBF on SBIs and cognitive changes

Background and Significance

Reduced cerebral blood flow (CBF) is known to contribute to cognitive changes in patients with severe carotid disease^{1, 2}. Whereas hypoperfusion and embolism have been viewed as dichotomous etiologies, there is a growing appreciation that they interact in the concept of the hemodynamic risk zone^{3,4}, namely border zone, region(s) of cortex that are vulnerable to decreased CBF. We believe that impaired washout is a mechanism that integrates hypoperfusion and embolization, specifically, poor clearance of emboli in regions of lower perfusion leads to increased incidence of SBIs. Understanding the interaction between CBF and microembolization will help to identify a group of patients at risk for baseline microembolization and those who are at risk for procedure-related microembolization. Therefore, appropriate patient consultation and management can be individualized.

Carotid revascularization is a commonly performed procedure for stroke prevention, but procedure-related SBIs due to microembolization are common, occurring in approximately 30-80% of patients who receive carotid revascularization procedures⁵⁻⁸. Although majority of these SBIs do not cause clinically evident neurologic sequelae, a subset of procedure-related SBIs is associated with cognitive deterioration^{6, 8, 9}. Understanding the cognitive effects of these microembolization-related SBIs and the dynamic relationship between CBF and SBIs has a significant impact in public health relating to cognitive impairment and risk of dementia in our aging population. Our **central hypothesis** is that characteristics of SBIs and CBF modulate cognitive impacts of procedure-related subclinical embolization.

Preliminary Data

1. Size and location of SBIs: Using the new semi-automated region-growing registration and algorithm program developed by our team, we analyzed previously recruited 157 subjects from 2012 to 2018. 77 subjects (49%) had procedure-related microinfarcts with an average volume of 762.90mm³ (18mm³ to 6892mm³) related to carotid interventions. We also evaluate the location of SBIs. Figure 1 showed sum of total lesion burden across all subjects by lobe and by subcortical gray matter structure. We observed that changes in volumes of infarcts were significantly correlated to long-term changes in episodic memory measured by Ray Auditory Verbal Learning

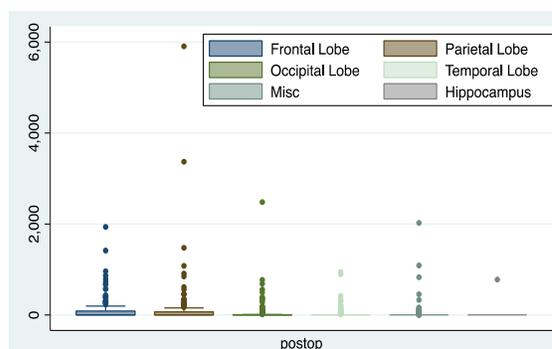


Figure 1: Box plot of distribution and volume of infarcts in brain regions. Misc: basal ganglia, thalamus, and amygdala. Lesions in both hemispheres are collapsed into a single side

Test (RAVLT) ($P < 0.05$) and executive function measured by the Trail Making Test ($P < 0.05$). When locations of SBIs were considered, there was a trend of correlations between SBI sizes and changes in some cognitive domains ($P < 0.05$).

2. **CBF analysis:** We analyzed ASL CBF of 16 subjects who underwent carotid interventions CBF maps were quantified. There is a significant increase in whole brain CBF immediately following interventions ($p < 0.01$). Although the CBF normalized at 6 months, there is a trend of improvement compared to preop ($P = 0.07$) (Figure 2).

3. **Cognitive measures:** We have evaluated cognitive function of subjects with severe carotid stenosis. Episodic memory was measured by RAVLT. After normalizing against age-matched Mayo's older Americans normative studies (MOANS) and group means, Z scores for RAVLT sum of the trial were shown to be lower ($Z = -0.79$, SD 1.3, CI: -1 to -0.53) than age-adjusted norm, suggesting impaired baseline episodic memory. We also observed a significant improvement in memory scores post-carotid interventions at 1 month and 6 months compared to the preop baseline. The score return to, but slightly higher than the baseline at 12 months. Despite an overall improvement in memory scores postop, approximately one-third of subjects experienced significant ($> 10\%$) postop memory decline and we believe that procedure-related SBIs contribute to decline in this group of patients.

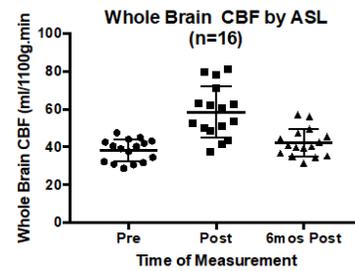


Figure 2: CBF changes of 16 subjects who underwent carotid interventions

Experimental Designs and Methods

Aim 1. Identify the characteristics of SBI that affect cognition: we will first capitalize our already collected longitudinal cognitive information (memory, executive function, motor, and language) to identify characters (locations and sizes) of SBIs that significantly affect cognitive changes at 1 and 6 months after carotid interventions through statistical modelling. Then, we will then prospectively recruit 15 subjects who undergo carotid revascularization procedures for severe atherosclerotic disease to validate the findings.

Aim 2. Determine the impact of CBF on SBIs and cognitive changes: We will first correlate CBF of the subjects in preliminary 2 with the frequency of SBIs and cognitive changes. The same prospectively recruited 15 subjects as in Aim 1 will also receive preop and 6 months postop MRI with ASL sequence. We will quantify whole brain and regional ASL CBF, and determine the impacts of preop CBF on SBIs and cognitive 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. These preliminary data is critical for our NIH grant application in next 18 months. We hope to identify MRI-based prognostic imaging biomarkers for cognitive significant SBIs and procedure-related long-term cognitive decline in the future. This project will also generate supplementary data on the cognitive effects of intraoperative flow reversal in carotid artery.

Year End Progress Summary

We have evaluated cognitive outcome of all patients who underwent carotid interventions in our database. All cognitive measures were normalized again age and education-matched control and compared at 4 time points: prior to intervention, 1 month, 6 months, and 12 months following interventions. We observed significant improvement in all cognitive domains. The results were presented at American Surgical Association, and the manuscript has been accepted for publication. The major findings are summarized in the tables below

Table 1: Overall MMSE is unchanged. However, there were significant less patients who had below average RAVLT scores post-carotid intervention compared with preop, suggesting carotid revascularization is associated with improved episodic memory. Parallel forms were used to mitigate practice effects

Summary of MMSE ≤27 by time points	
Time point	Frequency (%)
Pre-op (n=154)	57 (37.01%)
Post-op (n=121)	40 (33.06%)
6 months (n=90)	26 (28.89%)
12 months (n=76)	19 (25.00%)
Pre-op vs. Post-op (n=121)	47 (38.84%) vs. 40 (33.06%); p=0.25 ^a
Pre-op vs. 6 months (n=90)	32 (35.50%) vs. 26 (28.89%); p=0.26
Pre-op vs. 12 months (n=76)	26 (34.21%) vs. 19 (25.00%); p=0.19
Summary of RAVLTZ score<0 by time points	
Time point	Frequency (%)
Pre-op (n=147)	106 (72.11%)
Post-op (n=118)	78 (66.10%)
6 months (n=87)	47 (54.02%)
12 months (n=73)	46 (63.01%)
Pre-op vs. Post-op (n=118)	88 (74.58%) vs. 78 (66.10%); p<0.05 ^a
Pre-op vs. 6 months (n=87)	59 (67.82%) vs. 47 (54.02%); p=0.01
Pre-op vs. 12 months (n=73)	49 (67.12%) vs. 46 (63.01%); p=0.51

Table 2: All other cognitive measures were also normalized and compared. There is a consistent improvement across all cognitive measures at 1, 6, and 12 months following carotid interventions compared to preop.

Cognitive measures	N	Preop Mean± SD(CI)	Postop Mean ± SD(CI)	P-value
Preop vs. 1 month postop				
WAISE III-Digit Span	133	10.38 ± 2.76 (9.9-10.85)	10.65 ± 2.72 (10.08-11.11)	0.077
WAISEIII- Letter/Number	104	8.45 ± 3.44(7.78-9.12)	9.09 ± 3.06(8.49-9.68)	0.016
TMT -A	132	7.74 ± 3.09(7.21-8.27)	8.41 ± 3.20(7.86-8.96)	<0.001
TMT- B	126	7.92 ± 3.06(7.38-8.46)	8.54 ± 3.04(8-9.08)	0.003
BNT	120	10.78 ± 2.75(10.28-11.27)	10.28 ± 2.86(9.77-10.80)	0.001
GDS	127	7.51 ± 6.12(6.44-8.59)	6.72 ± 6.13(5.65-7.80)	0.015
Preop vs. 6 months postop				
Digit Span	99	10.54 ± 3.02(9.93-11.14)	11.12 ± 2.81(10.56-11.68)	0.011
Letter/number	83	8.92 ± 3.29(8.20-9.64)	9.59 ± 3.00(8.94-10.25)	0.028
TMT -A	98	8.07 ± 3.33(7.40-8.74)	8.94 ± 3.40(8.26-9.62)	0.001
TMT- B	97	8.12 ± 3.10(7.50-8.75)	8.86 ± 2.90(8.27-9.44)	0.005
BNT	92	10.22 ± 3.14(9.57-10.87)	10.95 ± 3.06(10.31-11.58)	<0.001
GDS	97	7.42 ± 6.20(6.17-8.67)	7.24 ± 6.41(5.94-8.53)	0.656
Preop vs. 12 months postop				
Digit Span	87	10.37 ± 2.76(9.78-10.96)	11.05 ± 2.90(10.43-11.67)	0.002
Letter/number	63	8.52 ± 3.47(7.65-9.40)	9.37 ± 3.66(8.44-10.29)	0.043
TMT -A	81	7.79 ± 3.02(7.12-8.46)	9.07 ± 3.48(8.30-9.85)	<0.001
TMT- B	80	7.93 ± 3.06(7.24-8.61)	8.68 ± 3.37(7.92-9.43)	0.016
BNT	78	10.45 ± 2.97(9.78-11.12)	11.26 ± 2.66(10.66-11.86)	<0.001
GDS	82	7.73 ± 5.81(6.45-9.01)	6.84 ± 6.14(5.49-8.19)	0.087

**UNIVERSITY OF ARIZONA
COLLEGE OF MEDICINE – PHOENIX
PROJECT PROGRESS REPORTS**

ARIZONA ALZHEIMER'S CONSORTIUM 2021-2022 Scientific Progress Report

Microglia gene expression, tracking inflammation, and monitoring cerebrovasculature.

Jonathan Lifshitz, PhD, Katherine R. Giordano, Luisa M. Rojas Valencia, Daniel R. Griffiths.
University of Arizona College of Medicine – Phoenix; Phoenix VA Health Care System; Arizona Alzheimer's Consortium.

Specific Aims:

1. To analyze gene expression of activated microglia variants using spatial genomics to determine subclasses beyond morphology. *Hypothesis: Microglia activation states based on morphology may include multiple subclasses as evident in gene expression profiles.*
2. To quantify fecal microbiome abundance and diversity in relation to peripheral inflammation after diffuse brain injury. *Hypothesis: Fecal microbiome diversity is proportionate to peripheral inflammation associated with diffuse brain injury.*
3. To develop quantification protocols for blood brain permeability and pharmacokinetics based on fluorolabeled compounds using miniature microscopes in mice.

Background and Significance:

[1] Microglia heterogeneity and the differential roles in health and disease are at the forefront of understanding and then treating disease. Single cell analysis routinely identifies gene expression clusters; histological analysis reports on various morphologies. New spatial transcriptomics can merge these analyses by quantifying gene expression in visually targeted regions. Of particular note, one microglia variant, the rod microglia has been overlooked since no molecular tools exist to distinguish them. Gene expression associated with rod microglia can identify a panel of known or unknown genes to enhance single-cell analysis and future investigation.

[2] Neurological disease, including traumatic brain injury (TBI), has neuroinflammation and peripheral inflammation as hallmarks of the disease process. Using blood flow cytometry, monocyte and neutrophil populations represent the peripheral immune response. Also, the microbiota of the gastrointestinal system is affected by disease, and a potential therapeutic target. To advance the field, we pursue a reliable, non-invasive pharmacodynamic outcome measures to track disease processes. Therefore, peripheral inflammation and fecal microbiome can be used as disease and therapeutic biomarkers.

[3] Cerebral pharmacokinetics measure novel compound brain penetrance as a function of time and administration. Our miniature microscope (miniscope) technology can image fluorescent molecules through a cranial window in rodents to observe vascular recruitment, compound bio-availability, and clearance. Using penetrable (fluoro-2-deoxyglucose) and impenetrable (fluoro-dextran) standards, the pharmacokinetics of novel compounds can be assessed. Analytical quantifications are necessary to validate the approach.

Preliminary Data, Experimental Design and Methods:

[1] *Ex vivo* phage display identified specific, high confidence domain antibody motifs of rod microglia, using whole brain tissue as a negative screen. In separate cohorts of brain-injured CX3CR1-eGFP mice, laser capture microdissected rod microglia were used in three positive screening rounds with the selective phage libraries biased towards rod microglia. To identify dAb biomarker candidates from the biopanning process, next generation sequencing (NGS) of the final library identified the biological motifs fused to the phage genome, using commercial sequence alignment software. Sequencing clusters were converted to amino acid sequences as a basis for single chain variable fragment antibodies against rod microglia. In addition to phage--derived synthetic antibodies, the approach pursues gene expression of rod microglia using spatial

transcriptomics. The 10X Genomics and nanoString spatial genomics platforms were used to visualize and then isolate rod microglia. It became apparent that the 10x Genomics platform was not developed enough to use mouse tissue for this study. Ongoing work uses nanoString DSP technology to visualize, transcribe, and sequence genes associated with rod microglia pathology. The research team works with nanoString technical support to optimize visualization and transcript preservation for analysis. Once visualized, the spatial transcriptomics will deliver gene expression results to achieve the proposed aim.

[2] The abundance and diversity of the fecal microbiome serves as a pharmacodynamic endpoint to monitor post-injury inflammation. From frozen fecal pellets, bacterial DNA will be extracted for PCR amplification of the 16S rRNA gene V3 region. RNAseq read sequences are analyzed for the richness and evenness of species as represented by the Shannon diversity index. Also, flow cytometry tracks leukocytes (monocytes, neutrophils) as population distributions shifting in response to injury, time, and sex in blood drawn repeatedly from the submandibular vein. New unsupervised analysis pathways reduce the dimensionality and cluster data to identify unique patterns in the data.

[3] Miniature microscopes visualize fluorescent compounds in the cortex under a cranial window. Ongoing studies determine route of administration profiles for fluorescent-tagged inert and novel compounds. These data are used to establish dosing strategies (e.g., route, dose interval) based on brain bioavailability. Fluoro-2-deoxyglucose is a positive control for rapid brain uptake. Fluorescent dextrans are a negative control for vascular labeling. At this time, quantification approaches are crude. Image processing algorithms will be developed and refined to quantify bioavailability and administration timing.

Proposed One-Year and Long-Term Outcomes:

Ms. Giordano is the lead on Aim 1 to detect rod microglia with phage-derived synthetic antibodies and develop spatial genomics protocols. We anticipate successful protocols with two different synthetic antibodies to be used on rodent and human tissue. We anticipate refined protocols for spatial genomics using commercial platforms.

Ms. Rojas is the lead on Aim 2 to track inflammation and microbiome diversity. She has gained expertise in the laboratory techniques. It is anticipated that samples are collected within 1 year and then analysis protocols can begin. Longitudinal measures over 3 weeks are proposed to track changes in peripheral inflammation and microbiome diversity after diffuse brain injury.

Mr. Griffiths is the lead on Aim 3 to analyze data from miniscopes. The video imaging is expected to be completed within the first quarter. Ongoing analysis techniques will be deployed throughout the funding period. Long term goals include the analysis of additional study designs to evaluate cerebrovascular function.

The long-term outcomes include a validated and verified set of molecular tools (antibodies, genes) for rod microglia. The goal is to apply these tools to diagnostic markers in the blood to detect rod microglia presence in the course of disease. In the treatment of injury and age-related neurodegenerative disease, pharmacodynamic biomarkers are necessary to evaluate therapeutic efficacy of treatment interventions, such as probiotic interventions to modulate inflammation. Miniscopes will advance the technologies available to view the brain and function.

Year End Progress Summary:

[1] The synthetic antibodies for rod microglia are based on a proposed antibody structure from human fragments. To optimize success, the same tissue preparation procedures for phage display have been used to validate the antibodies. To date, none of the antigen retrieval, tissue permeabilization, or solution concentrations have delivered specific results. During the funding period, supply chain and key personnel availability limited opportunities to prepare new lots of synthetic antibodies. Brain tissue is on hand to validate new synthetic antibodies when synthetic antibodies become available.

Gene expression unique to rod microglia can unlock a new class, and potential subclasses, of microglia to develop a framework of neuroinflammation in aging, injury, and disease. We deployed state-of-the-art spatial transcriptomics to quantify gene expression from brain regions inhabited by rod microglia. Despite ongoing support from 10x Genomics, their products were not compatible with the standard tissue processing and visualization of rod microglia. The tradeoff between visualization and RNA integrity was never achieved. In the funding period, access to nanoString DSP technology became available, which can accomplish the goal with degraded RNA. Initial attempts to visualize rod microglia were successful and protocol refinement continues. Availability of technical support and access to the equipment are immediate next steps to sequence rod microglia gene expression. Rod microglia gene expression profiles will be used to reanalyze published single cell microglia gene expression databases.

Ongoing grant submissions to the DOD, NIH, and VA are in constant revision to support the rod microglia studies. The most recent NIH R01 submission is indicated as an AD/ADRD submission and received a 15th percentile following grant review.

[2] The focus of peripheral immune monitoring has been on flow cytometry. The analysis software (FlowJo) now permits improved compensation and unsupervised analysis using machine learning approaches. The analytical pipeline now removes the subjectivity associated with flow cytometry and may identify unique cell type clusters in studies of the estrous cycle, brain injury, and response to probiotic treatment. At the same time, the *in vivo* study was completed to compare peripheral brain injury responses in terms of circulating lymphocytes and fecal microbiome as influenced by probiotic delivery. All samples were collected and processed. In the course of analysis, Ms. Rojas was selected as a University of Arizona Data Science Fellow, where they were introduced to data management, analysis, and visualization necessary for these complex data. At the conclusion of the funding period, all samples are collected and analysis strategies defined. The next funding period will complete the analyses.

[3] Our research team has advanced technical capability to build, modify, implant, and use miniscopes to visualize brain dynamics during naturalistic behavior. In the funding period, we used miniscopes to determine the route of administration for novel nanoparticles, which guided the therapeutic strategy in a mouse model of cerebral stroke. 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. These protocols will inform new understanding of cerebrovascular dynamics in response to naturalistic behavior (e.g., sleep, estrous cycling) and injury (e.g., cumulative closed head injury). Based on these methods, a new NIH R21 has been submitted for funding.

Outside the scope of the Arizona Alzheimer's Consortium project, our research team continues to work on a 4-year study on the chronic cognitive deficits associated with diffuse TBI in the rat, exploring cardiovascular comorbidities. These studies are funded by a VA Merit Award, in conjunction with Raymond Migrino, MD. Our model continues to reproduce the cognitive impairments in TBI survivors, which are associated with reduced cerebrovascular reactivity at 6 months after injury and may contribute to vascular dementia.



2021 – 2022
Publications & Manuscripts

Abbasloo E, Abdollahi F, Saberi A, Esmaeili-Mahani S, Kaeidi A, Akhlaghinasab F, Sheibani V, Thomas TC, Kobeissy FH, Oryan S. Involvement of T-type calcium channels in the mechanism of low dose morphine-induced hyperalgesia in adult male rats. *Neuropeptides*. 2021 Dec;90:102185. doi: 10.1016/j.npep.2021.102185. Epub 2021 Aug 14. PMID: 34419803.

Acosta-Uribe J, Aguillón D, Cochran JN, Giraldo M, Madrigal L, Killingsworth BW, Singhal R, Labib S, Alzate D, Velilla L, Moreno S, García GP, Saldarriaga A, Piedrahita F, Hincapié L, López HE, Perumal N, Morelo L, Vallejo D, Solano JM, Reiman EM, Surace EI, Itzcovich T, Allegri R, Sánchez-Valle R, Villegas-Lanau A, White CL 3rd, Matallana D, Myers RM, Browning SR, Lopera F, Kosik KS. A neurodegenerative disease landscape of rare mutations in Colombia due to founder effects. *Genome Med*. 2022 Mar 8;14(1):27. doi: 10.1186/s13073-022-01035-9. PMCID: PMC8902761.

Adams AC, Borden ES, Macy AM, Thomson N, Cui H, Gimbel MI, Wilson MA, Buetow KH, Roe DJ, DiCaudo DJ, Homsí J, Hastings KT. High GILT Expression Is Associated with Improved Survival in Metastatic Melanoma Patients Treated with Immune Checkpoint Inhibition. *Cancers (Basel)*. 2022 Apr 28;14(9):2200. doi: 10.3390/cancers14092200. PMCID: PMC9100272.

Adler CH, Beach TG, Zhang N, Shill HA, Driver-Dunckley E, Mehta SH, Atri A, Caviness JN, Serrano G, Shprecher DR, Sue LI, Belden CM. Clinical Diagnostic Accuracy of Early/Advanced Parkinson Disease: An Updated Clinicopathologic Study. *Neurol Clin Pract*. 2021 Aug;11(4):e414-e421. doi: 10.1212/CPJ.0000000000001016. PMID: 34484939.

Ahmad S, Truran S, Karamanova N, Kindelin A, Lozoya M, Weissig V, Emerson H, Griffiths DR, Vail T, Lifshitz J, Ducruet AF, Migrino RQ. Nanoliposomes Reduce Stroke Injury Following Middle Cerebral Artery Occlusion in Mice. *Stroke*. 2022 Feb;53(2):e37-e41. doi: 10.1161/STROKEAHA.121.037120. Epub 2021 Nov 8. PMID: 34743535.

Ahn S, Mathiason MA, Yu F. Longitudinal Cognitive Profiles by Anxiety and Depressive Symptoms in American Older Adults With Subjective Cognitive Decline. *J Nurs Scholarsh*. 2021 Nov;53(6):698-708. doi: 10.1111/jnu.12692. Epub 2021 Aug 3. PMCID: PMC8599627.

Alabsi W, Acosta MF, Al-Obeidi FA, Hay M, Polt R, Mansour HM. Synthesis, Physicochemical Characterization, In Vitro 2D/3D Human Cell Culture, and In Vitro Aerosol Dispersion Performance of Advanced Spray Dried and Co-Spray Dried Angiotensin (1-7) Peptide and PNA5 with Trehalose as Microparticles/Nanoparticles for Targeted Respiratory Delivery as Dry Powder Inhalers. *Pharmaceutics*. 2021 Aug 17;13(8):1278. doi: 10.3390/pharmaceutics13081278. PMCID: PMC8398878.

Alexander RC, Raudibaugh K, Spierings ELH, Katz N. A 3-way Cross-over Study of Pregabalin, Placebo, and the Histamine 3 Receptor Inverse Agonist AZD5213 in Combination With Pregabalin in Patients With Painful Diabetic Neuropathy and Good Pain-reporting Ability. *Clin J Pain*. 2021 Jan;37(1):38-42. doi: 10.1097/AJP.0000000000000886. PMID: 33086238.

Alosco ML, Tripodis Y, Baucom ZH, Adler CH, Balcer LJ, Bernick C, Mariani ML, Au R, Banks SJ, Barr WB, Wethe JV, Cantu RC, Coleman MJ, Dodick DW, McClean MD, McKee AC, Mez J, Palmisano JN, Martin B, Hartlage K, Lin AP, Koerte IK, Cummings JL, Reiman EM, Stern RA, Shenton ME, Bouix S; DIAGNOSE CTE Research Project. White matter hyperintensities in former American football players. *Alzheimers Dement*. 2022 Aug 22. doi: 10.1002/alz.12779. Epub ahead of print. PMID: 35996231.

Alsop E, Meechoovet B, Kitchen R, Sweeney T, Beach TG, Serrano GE, Hutchins E, Ghiran I, Reiman R, Syring M, Hsieh M, Courtright-Lim A, Valkov N, Whitsett TG, Rakela J, Pockros P, Rozowsky J, Gallego J, Huentelman MJ, Shah R, Nakaji P, Kalani MYS, Laurent L, Das S, Van Keuren-Jensen K. A Novel Tissue Atlas and Online Tool for the Interrogation of Small RNA Expression in Human Tissues and Biofluids. *Front Cell Dev Biol.* 2022 Mar 4;10:804164. doi: 10.3389/fcell.2022.804164. PMID: PMC8934391.

Ambadi PS, Basche K, Kosciak RL, Berisha V, Liss JM, Mueller KD. Spatio-Semantic Graphs From Picture Description: Applications to Detection of Cognitive Impairment. *Front Neurol.* 2021 Dec 9;12:795374. doi: 10.3389/fneur.2021.795374. PMID: PMC8696356.

An H, Tao W, Liang Y, Li P, Li M, Zhang X, Chen K, Wei D, Xie D, Zhang Z. Dengzhanxin Injection Ameliorates Cognitive Impairment Through a Neuroprotective Mechanism Based on Mitochondrial Preservation in Patients With Acute Ischemic Stroke. *Front Pharmacol.* 2021 Aug 30;12:712436. doi: 10.3389/fphar.2021.712436. eCollection 2021. PMID: 34526899

Andrews-Hanna JR, Woo CW, Wilcox R, Eisenbarth H, Kim B, Han J, Losin EAR, Wager TD. The conceptual building blocks of everyday thought: Tracking the emergence and dynamics of ruminative and nonruminative thinking. *J Exp Psychol Gen.* 2022 Mar;151(3):628-642. doi: 10.1037/xge0001096. Epub 2021 Sep 9. PMID: PMC8904643.

Arias JC, Edwards M, Vitali F, Beach TG, Serrano GE, Weinkauff CC. Extracranial carotid atherosclerosis is associated with increased neurofibrillary tangle accumulation. *J Vasc Surg.* 2022 Jan;75(1):223-228. doi: 10.1016/j.jvs.2021.07.238. Epub 2021 Aug 31. PMID: PMC8976507.

Assunção SS, Sperling RA, Ritchie C, Kerwin DR, Aisen PS, Lansdall C, Atri A, Cummings J. Meaningful benefits: a framework to assess disease-modifying therapies in preclinical and early Alzheimer's disease. *Alzheimers Res Ther.* 2022 Apr 19;14(1):54. doi: 10.1186/s13195-022-00984-y. PMID: 35440022.

Auer S, Haeltermann NA, Weissberger TL, Erlich JC, Susilaradeya D, Julkowska M, Gazda MA, Schwessinger B, Jadavji NM; Reproducibility for Everyone Team. A community-led initiative for training in reproducible research. *Elife.* 2021 Jun 21;10:e64719. doi: 10.7554/eLife.64719. PMID: PMC8282331.

Baker AT, Boyd RJ, Sarkar D, Teijeira-Crespo A, Chan CK, Bates E, Waraich K, Vant J, Wilson E, Truong CD, Lipka-Lloyd M, Fromme P, Vermaas J, Williams D, Machiesky L, Heurich M, Nagalo BM, Coughlan L, Umlauf S, Chiu PL, Rizkallah PJ, Cohen TS, Parker AL, Singharoy A, Borad MJ. ChAdOx1 interacts with CAR and PF4 with implications for thrombosis with thrombocytopenia syndrome. *Sci Adv.* 2021 Dec 3;7(49):eabl8213. doi: 10.1126/sciadv.abl8213. Epub 2021 Dec 1. PMID: PMC8635433.

Baloni P, Funk CC, Readhead B, Price ND. Systems modeling of metabolic dysregulation in neurodegenerative diseases. *Curr Opin Pharmacol.* 2021 Oct;60:59-65. doi: 10.1016/j.coph.2021.06.012. Epub 2021 Aug 2. PMID: PMC8511060.

Bauer K, Malek-Ahmadi M. Meta-analysis of Controlled Oral Word Association Test (COWAT) FAS performance in amnesic mild cognitive impairment and cognitively unimpaired older adults. *Appl Neuropsychol Adult.* 2021 Aug 15:1-7. doi: 10.1080/23279095.2021.1952590. Epub ahead of print. PMID: 34392761.

Beach TG. A History of Senile Plaques: From Alzheimer to Amyloid Imaging. *J Neuropathol Exp Neurol.* 2022 May 20;81(6):387-413. doi: 10.1093/jnen/nlac030. PMID: PMC9122832.

Beck JS, Madaj Z, Cheema CT, Kara B, Bennett DA, Schneider JA, Gordon MN, Ginsberg SD, Mufson EJ, Counts SE. Co-expression Network Analysis of Frontal Cortex during the Progression of Alzheimer's Disease. *Cereb Cortex.* 2022 Jan 24:bhac001. doi: 10.1093/cercor/bhac001. Epub ahead of print. PMID: 35076713.

Beitchman, JA*, J Lifshitz*, NG Harris, TC Thomas, AD Lafrenaye, A Hånell, CE Dixon, JT Povlishock, RK Rowe. (2021) Spatial Distribution of Neuropathology and Neuroinflammation Elucidate the Biomechanics of Fluid Percussion Injury. *Neurotrauma Reports* 2(1):59-75 PMID: 34223546. <https://doi.org/10.1089/neur.2020.0046>

Beitchman, JA, BA Burg, DM Sabb, AH Hosseini, J Lifshitz. (2022) The pentagram of concussion: an observational analysis that describes five overt indicators of head trauma. *BMC Sports Science, Medicine and Rehabilitation* 14(1):39 PMID: 35292090. <https://doi.org/10.1186/s13102-022-00430-4>

Bell LC, Fuentes AE, Healey DR, Chao R, Bakkar N, Sirianni RW, Medina DX, Bowser RP, Ladha SS, Semmineh NB, Stokes AM, Quarles CC. Longitudinal evaluation of myofiber microstructural changes in a preclinical ALS model using the transverse relaxivity at tracer equilibrium (TRATE): A preliminary study. *Magn Reson Imaging.* 2022 Jan;85:217-221. doi: 10.1016/j.mri.2021.10.036. Epub 2021 Oct 27. PMID: 34715291.

Bell RP, Meade CS, Gadde S, Towe SL, Hall SA, Chen NK. Principal component analysis denoising improves sensitivity of MR diffusion to detect white matter injury in neuroHIV. *J Neuroimaging.* 2022 May;32(3):544-553. doi: 10.1111/jon.12965. Epub 2022 Jan 12. PMID: PMC9090947.

Bellenguez C, Küçükali F, Jansen IE, Kleindam L, Moreno-Grau S, Amin N, Naj AC, Campos-Martin R, Grenier-Boley B, Andrade V, Holmans PA, Boland A, Damotte V, van der Lee SJ, Costa MR, Kuulasmaa T, Yang Q, de Rojas I, Bis JC, Yaqub A, Prokic I, Chapuis J, Ahmad S, Giedraitis V, Aarsland D, Garcia-Gonzalez P, Abdelnour C, Alarcón-Martín E, Alcolea D, Alegret M, Alvarez I, Álvarez V, Armstrong NJ, Tsolaki A, Antúnez C, Appollonio I, Arcaro M, Archetti S, Pastor AA, Arosio B, Athanasiu L, Bailly H, Banaj N, Baquero M, Barral S, Beiser A, Pastor AB, Below JE, Benček P, Benussi L, Berr C, Besse C, Bessi V, Binetti G, Bizarro A, Blesa R, Boada M, Boerwinkle E, Borroni B, Boschi S, Bossù P, Bråthen G, Bressler J, Bresner C, Brodaty H, Brookes KJ, Brusco LI, Buiza-Rueda D, Bürger K, Burholt V, Bush WS, Calero M, Cantwell LB, Chene G, Chung J, Cuccaro ML, Carracedo Á, Cecchetti R, Cervera-Carles L, Charbonnier C, Chen HH, Chillotti C, Ciccone S, Claassen JAHR, Clark C, Conti E, Corma-Gómez A, Costantini E, Custodero C, Daian D, Dalmaso MC, Daniele A, Dardiotis E, Dartigues JF, de Deyn PP, de Paiva Lopes K, de Witte LD, Dobbie S, Deckert J, Del Ser T, Denning N, DeStefano A, Dichgans M, Diehl-Schmid J, Diez-Fairen M, Rossi PD, Djurovic S, Duron E, Düzel E, Dufouil C, Eiriksdottir G, Engelborghs S, Escott-Price V, Espinosa A, Ewers M, Faber KM, Fabrizio T, Nielsen SF, Fardo DW, Farotti L, Fenoglio C, Fernández-Fuertes M, Ferrari R, Ferreira CB, Ferri E, Fin B, Fischer P, Fladby T, Fließbach K, Fongang B, Fornage M, Fortea J, Foroud TM, Fostinelli S, Fox NC, Franco-Macías E, Bullido MJ, Frank-García A, Froelich L, Fulton-Howard B, Galimberti D, García-Alberca JM, García-González P, Garcia-Madrona S, Garcia-Ribas G, Ghidoni R, Giegling I, Giorgio G, Goate AM, Goldhardt O, Gomez-Fonseca D, González-Pérez A, Graff C, Grande G, Green E, Grimmer T, Grünblatt E, Grunin M, Gudnason V, Guetta-Baranes T, Haapasalo A, Hadjigeorgiou G, Haines JL, Hamilton-Nelson KL, Hampel H, Hanon O, Hardy J, Hartmann AM,

Hausner L, Harwood J, Heilmann-Heimbach S, Helisalmi S, Heneka MT, Hernández I, Herrmann MJ, Hoffmann P, Holmes C, Holstege H, Vilas RH, Hulsman M, Humphrey J, Biessels GJ, Jian X, Johansson C, Jun GR, Kastumata Y, Kauwe J, Kehoe PG, Kilander L, Ståhlbom AK, Kivipelto M, Koivisto A, Kornhuber J, Kosmidis MH, Kukull WA, Kuksa PP, Kunkle BW, Kuzma AB, Lage C, Laukka EJ, Launer L, Lauria A, Lee CY, Lehtisalo J, Lerch O, Lleó A, Longstreth W Jr, Lopez O, de Munain AL, Love S, Löwemark M, Luckcuck L, Lunetta KL, Ma Y, Macías J, MacLeod CA, Maier W, Mangialasche F, Spallazzi M, Marquié M, Marshall R, Martin ER, Montes AM, Rodríguez CM, Masullo C, Mayeux R, Mead S, Mecocci P, Medina M, Meggy A, Mehrabian S, Mendoza S, Menéndez-González M, Mir P, Moebus S, Mol M, Molina-Porcel L, Montreal L, Morelli L, Moreno F, Morgan K, Mosley T, Nöthen MM, Muchnik C, Mukherjee S, Nacmias B, Ngandu T, Nicolas G, Nordestgaard BG, Olaso R, Orellana A, Orsini M, Ortega G, Padovani A, Paolo C, Papenberg G, Parnetti L, Pasquier F, Pastor P, Peloso G, Pérez-Cordón A, Pérez-Tur J, Pericard P, Peters O, Pijnenburg YAL, Pineda JA, Piñol-Ripoll G, Pisanu C, Polak T, Popp J, Posthuma D, Priller J, Puerta R, Quenez O, Quintela I, Thomassen JQ, Rábano A, Rainero I, Rajabli F, Ramakers I, Real LM, Reinders MJT, Reitz C, Reyes-Dumeyer D, Ridge P, Riedel-Heller S, Riederer P, Roberto N, Rodriguez-Rodriguez E, Rongve A, Allende IR, Rosende-Roca M, Royo JL, Rubino E, Rujescu D, Sáez ME, Sakka P, Saltvedt I, Sanabria Á, Sánchez-Arjona MB, Sanchez-Garcia F, Juan PS, Sánchez-Valle R, Sando SB, Sarnowski C, Satizabal CL, Scamosci M, Scarmeas N, Scarpini E, Scheltens P, Scherbaum N, Scherer M, Schmid M, Schneider A, Schott JM, Selbæk G, Seripa D, Serrano M, Sha J, Shadrin AA, Skrobot O, Slifer S, Snijders GJL, Soininen H, Solfrizzi V, Solomon A, Song Y, Sorbi S, Sotolongo-Grau O, Spalletta G, Spottke A, Squassina A, Stordal E, Tartan JP, Tárrega L, Tesí N, Thalamuthu A, Thomas T, Tosto G, Traykov L, Tremolizzo L, Tybjærg-Hansen A, Uitterlinden A, Ullgren A, Ulstein I, Valero S, Valladares O, Broeckhoven CV, Vance J, Vardarajan BN, van der Lugt A, Dongen JV, van Rooij J, van Swieten J, Vandenberghe R, Verhey F, Vidal JS, Vogelgsang J, Vyhnaek M, Wagner M, Wallon D, Wang LS, Wang R, Weinhold L, Wiltfang J, Windle G, Woods B, Yannakoulia M, Zare H, Zhao Y, Zhang X, Zhu C, Zulaica M; EADB; GR@ACE; DEGESCO; EADI; GERAD; Demgene; FinnGen; ADGC; CHARGE, Farrer LA, Psaty BM, Ghanbari M, Raj T, Sachdev P, Mather K, Jessen F, Ikram MA, de Mendonça A, Hort J, Tsolaki M, Pericak-Vance MA, Amouyel P, Williams J, Frikke-Schmidt R, Clarimon J, Deleuze JF, Rossi G, Seshadri S, Andreassen OA, Ingelsson M, Hiltunen M, Sleegers K, Schellenberg GD, van Duijn CM, Sims R, van der Flier WM, Ruiz A, Ramirez A, Lambert JC. New insights into the genetic etiology of Alzheimer's disease and related dementias. *Nat Genet.* 2022 Apr;54(4):412-436. doi: 10.1038/s41588-022-01024-z. Epub 2022 Apr 4. PMID: PMC9005347.

Bennett C, Green J, Ciancio M, Goral J, Pitstick L, Pytynia M, Meyer A, Kwatra N, Jadavji NM. Dietary folic acid deficiency impacts hippocampal morphology and cortical acetylcholine metabolism in adult male and female mice. *Nutr Neurosci.* 2021 May 27:1-9. doi: 10.1080/1028415X.2021.1932242. Epub ahead of print. PMID: 34042561.

Bergamino M, Burke A, Baxter LC, Caselli RJ, Sabbagh MN, Talboom JS, Huentelman MJ, Stokes AM. Longitudinal Assessment of Intravoxel Incoherent Motion Diffusion-Weighted MRI Metrics in Cognitive Decline. *J Magn Reson Imaging.* 2022 Mar 23. doi: 10.1002/jmri.28172. Epub ahead of print. PMID: 35319142.

Bergamino M, Keeling EG, Baxter LC, Sisco NJ, Walsh RR, Stokes AM. Sex Differences in Alzheimer's Disease Revealed by Free-Water Diffusion Tensor Imaging and Voxel-Based Morphometry. *J Alzheimers Dis.* 2022;85(1):395-414. doi: 10.3233/JAD-210406. PMID: 35319142.

Bergamino M, Schiavi S, Daducci A, Walsh RR, Stokes AM. Analysis of Brain Structural Connectivity Networks and White Matter Integrity in Patients With Mild Cognitive Impairment. *Front Aging Neurosci.* 2022 Jan 31;14:793991. doi: 10.3389/fnagi.2022.793991. PMC8842680.

Bernaude VE, Bulen HL, Peña VL, Koebele SV, Northup-Smith SN, Manzo AA, Valenzuela Sanchez M, Opachich Z, Ruhland AM, Bimonte-Nelson HA. Task-dependent learning and memory deficits in the TgF344-AD rat model of Alzheimer's disease: three key timepoints through middle-age in females. *Sci Rep.* 2022 Aug 26;12(1):14596. doi: 10.1038/s41598-022-18415-1. PMID: 36028737.

Bernstein AS, Rapcsak SZ, Hornberger M, Saranathan M; Alzheimer's Disease Neuroimaging Initiative. Structural Changes in Thalamic Nuclei Across Prodromal and Clinical Alzheimer's Disease. *J Alzheimers Dis.* 2021;82(1):361-371. doi: 10.3233/JAD-201583. PMID: 34024824.

Bhatia K, Kindelin A, Nadeem M, Khan MB, Yin J, Fuentes A, Miller K, Turner GH, Preul MC, Ahmad AS, Mufson EJ, Waters MF, Ahmad S, Ducruet AF. Complement C3a Receptor (C3aR) Mediates Vascular Dysfunction, Hippocampal Pathology, and Cognitive Impairment in a Mouse Model of VCID. *Transl Stroke Res.* 2022 Oct;13(5):816-829. doi: 10.1007/s12975-022-00993-x. Epub 2022 Mar 8. PMID: 35258803.

Bhattacharya D, Becker C, Readhead B, Goossens N, Novik J, Fiel MI, Cousens LP, Magnusson B, Backmark A, Hicks R, Dudley JT, Friedman SL. Repositioning of a novel GABA-B receptor agonist, AZD3355 (Lesogaberan), for the treatment of non-alcoholic steatohepatitis. *Sci Rep.* 2021 Oct 21;11(1):20827. doi: 10.1038/s41598-021-99008-2. PMCID: PMC8531016.

Billingsley KJ, Alvarez Jerez P, Grenn FP, Bandres-Ciga S, Malik L, Hernandez D, Torkamani A, Ryten M, Hardy J; United Kingdom Brain Expression Consortium (UKBEC), Scholz SW, Traynor BJ, Dalgard CL, Ehrlich DJ, Tanaka T, Ferrucci L, Beach TG, Serrano GE, Ding J, Gibbs JR, Blauwendraat C, Singleton AB. Profiling the NOTCH2NL GGC Repeat Expansion in Parkinson's Disease in the European Population. *Mov Disord.* 2022 Jul 22. doi: 10.1002/mds.29155. Epub ahead of print. PMID: 35866887.

Bjorklund, GR, Anderson, TR, Stabenfeldt, SE. Recent advances in stem cell therapies to address neuroinflammation, stem cell survival, and the need for rehabilitative therapies to treat traumatic brain injuries. *International Journal of Molecular Sciences.* 2021; 22(4):1978. DOI: 10.3390/ijms22041978. PMCID: PMC7922668.

Blauwendraat C, Iwaki H, Makarious MB, Bandres-Ciga S, Leonard HL, Grenn FP, Lake J, Krohn L, Tan M, Kim JJ, Gibbs JR, Hernandez DG, Ruskey JA, Pihlstrøm L, Toft M, van Hilten JJ, Marinus J, Schulte C, Brockmann K, Sharma M, Siitonen A, Majamaa K, Eerola-Rautio J, Tienari PJ, Grosset DG, Lesage S, Corvol JC, Brice A, Wood N, Hardy J, Gan-Or Z, Heutink P, Gasser T, Morris HR, Noyce AJ, Nalls MA, Singleton AB; International Parkinson's Disease Genomics Consortium (IPDGC). Investigation of Autosomal Genetic Sex Differences in Parkinson's Disease. *Ann Neurol.* 2021 Jul;90(1):35-42. doi: 10.1002/ana.26090. Epub 2021 May 24. PMCID: PMC8422907.

Bleakley A, Hennessy M, Maloney E, Young DG, Crowley J, Silk K, Langbaum JB. Psychosocial Determinants of COVID-19 Vaccination Intention Among White, Black, and Hispanic Adults in the US. *Ann Behav Med.* 2022 Apr 2;56(4):347-356. doi: 10.1093/abm/kaab091. PMID: 34596660.

Bleakley A, Maloney EK, Harkins K, Nelson MN, Akpek E, Langbaum JB. An Elicitation Study to Understand Black, Hispanic, and Male Older Adults' Willingness to Participate in Alzheimer's Disease-Focused Research Registries. *J Alzheimers Dis*. 2022 Jul 5. doi: 10.3233/JAD-220196. Epub ahead of print. PMID: 35811525.

Bokulich NA, Łaniewski P, Adamov A, Chase DM, Caporaso JG, Herbst-Kralovetz MM. Multi-omics data integration reveals metabolome as the top predictor of the cervicovaginal microenvironment. *PLoS Comput Biol*. 2022 Feb 23;18(2):e1009876. doi: 10.1371/journal.pcbi.1009876. PMID: PMC8901057.

Bordeaux SJ, Baca AW, Begay RL, Gachupin FC, Caporaso JG, Herbst-Kralovetz MM, Lee NR. Designing Inclusive HPV Cancer Vaccines and Increasing Uptake among Native Americans-A Cultural Perspective Review. *Curr Oncol*. 2021 Sep 24;28(5):3705-3716. doi: 10.3390/currncol28050316. PMID: PMC8482231.

Borden ES, Adams AC, Buetow KH, Wilson MA, Bauman JE, Curiel-Lewandrowski C, Chow HS, LaFleur BJ, Hastings KT. Shared Gene Expression and Immune Pathway Changes Associated with Progression from Nevi to Melanoma. *Cancers (Basel)*. 2021 Dec 21;14(1):3. doi: 10.3390/cancers14010003. PMID: PMC8749980.

Borden ES, Buetow KH, Wilson MA, Hastings KT. Cancer Neoantigens: Challenges and Future Directions for Prediction, Prioritization, and Validation. *Front Oncol*. 2022 Mar 3;12:836821. doi: 10.3389/fonc.2022.836821. PMID: PMC8929516.

Borden ES, Ghafoor S, Buetow KH, LaFleur BJ, Wilson MA, Hastings KT. NeoScore Integrates Characteristics of the Neoantigen:MHC Class I Interaction and Expression to Accurately Prioritize Immunogenic Neoantigens. *J Immunol*. 2022 Apr 1;208(7):1813-1827. doi: 10.4049/jimmunol.2100700. Epub 2022 Mar 18. PMID: PMC8983234.

Borsom, Emily M., Christopher R. Keefe, Allyson H. Hirsch, Gabrielle M. Orsini, Kathryn A. Conn, Sierra A. Jaramillo, George Testo, Melanie Palma Avila, Evan K. Bolyen, Matthew R. Dillon, J. Gregory Caporaso, and Emily K. Cope. 2021. "A Longitudinal Study of the Unique Gut Microbiota of 3xTg-AD Mice Modeling Key AD Pathologies." *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* 17: e054633. <https://doi.org/10.1002/alz.054633> *Abstract

Borsom, Emily M., Kathryn Conn, Christopher R. Keefe, Chloe Herman, Gabrielle M. Orsini, Allyson H. Hirsch, Melanie Palma Avila, George Testo, Sierra A. Jaramillo, Evan Bolyen, J. Gregory Caporaso, and Emily K. Cope. 2022. "Predicting Neurodegenerative Disease Using Pre-Pathology Gut Microbiota Composition: A Longitudinal Study in Mice Modeling Alzheimer's Disease Pathologies." doi: 10.21203/rs.3.rs-1538737/v1.

Bouchareychas L, Duong P, Phu TA, Alsop E, Meechoovet B, Reiman R, Ng M, Yamamoto R, Nakauchi H, Gasper WJ, Van Keuren-Jensen K, Raffai RL. High glucose macrophage exosomes enhance atherosclerosis by driving cellular proliferation & hematopoiesis. *iScience*. 2021 Jul 10;24(8):102847. doi: 10.1016/j.isci.2021.102847. PMID: PMC8333149.

Boutzoukas EM, O'Shea A, Kraft JN, Hardcastle C, Evangelista ND, Hausman HK, Albizu A, Van Etten EJ, Bharadwaj PK, Smith SG, Song H, Porges EC, Hishaw A, DeKosky ST, Wu SS, Marsiske M, Alexander GE, Cohen R, Woods AJ. Higher white matter hyperintensity load adversely affects pre-post proximal cognitive training performance in healthy older adults. *Geroscience*. 2022 Jun;44(3):1441-1455. doi: 10.1007/s11357-022-00538-y. Epub 2022 Mar 12. PMID: PMC9213634.

Bouwer FL, Nityananda V, Rouse AA, Ten Cate C. Rhythmic abilities in humans and non-human animals: a review and recommendations from a methodological perspective. *Philos Trans R Soc Lond B Biol Sci.* 2021 Oct 11;376(1835):20200335. doi: 10.1098/rstb.2020.0335. Epub 2021 Aug 23. PMID: PMC8380979.

Boyd RJ, Olson TL, Zook JD, Stein D, Aceves M, Lin WH, Craciunescu FM, Hansen DT, Anastasiadis PZ, Singharoy A, Fromme P. Characterization and computational simulation of human Syx, a RhoGEF implicated in glioblastoma. *FASEB J.* 2022 Jul;36(7):e22378. doi: 10.1096/fj.202101808RR. PMID: PMC9262375.

Branigan GL, Torrandell-Haro G, Soto M, Gelmann EP, Vitali F, Rodgers KE, Brinton RD. Androgen-targeting therapeutics mitigate the adverse effect of GnRH agonist on the risk of neurodegenerative disease in men treated for prostate cancer. *Cancer Med.* 2022 Jul;11(13):2687-2698. doi: 10.1002/cam4.4650. Epub 2022 Mar 16. PMID: PMC9249980.

Bray EE, Raichlen DA, Forsyth KK, Promislow DEL, Alexander GE, MacLean EL, Dog Aging Project. (2022) Associations between physical activity and cognitive dysfunction in older companion dogs: Results from the Dog Aging Project. *Geroscience*, provisionally accepted.

Bray EE, Raichlen DA, Forsyth KK, Promislow DEL, Alexander GE, MacLean EL, Dog Aging Project. (2022) Associations between physical activity and cognitive dysfunction in older companion dogs: Results from the Dog Aging Project, submitted.

Brister D, Werner BA, Gideon G, McCarty PJ, Lane A, Burrows BT, McLees S, Adelson PD, Arango JI, Marsh W, Flores A, Pankratz MT, Ly NH, Flood M, Brown D, Carpentieri D, Jin Y, Gu H, Frye RE. Central Nervous System Metabolism in Autism, Epilepsy and Developmental Delays: A Cerebrospinal Fluid Analysis. *Metabolites.* 2022 Apr 20;12(5):371. doi: 10.3390/metabo12050371. PMID: PMC9148155.

Brown AL, Wilkins OG, Keuss MJ, Hill SE, Zanovello M, Lee WC, Bampton A, Lee FCY, Masino L, Qi YA, Bryce-Smith S, Gatt A, Hallegger M, Fagegaltier D, Phatnani H; NYGC ALS Consortium, Newcombe J, Gustavsson EK, Seddighi S, Reyes JF, Coon SL, Ramos D, Schiavo G, Fisher EMC, Raj T, Secrier M, Lashley T, Ule J, Buratti E, Humphrey J, Ward ME, Fratta P. TDP-43 loss and ALS-risk SNPs drive mis-splicing and depletion of UNC13A. *Nature.* 2022 Mar;603(7899):131-137. doi: 10.1038/s41586-022-04436-3. Epub 2022 Feb 23. PMID: PMC8891020.

Buhlman LM, Krishna G, Jones TB, Thomas TC. *Drosophila* as a model to explore secondary injury cascades after traumatic brain injury. *Biomed Pharmacother.* 2021 Oct;142:112079. doi: 10.1016/j.biopha.2021.112079. Epub 2021 Aug 27. PMID: PMC8458259.

Burke AD, Apostolova L. Talking With Patients and Care Partners About Treatment Goals and Challenges in Early-Stage Alzheimer Disease. *J Clin Psychiatry.* 2021 May 11;82(3):BG20044WC2C. doi: 10.4088/JCP.BG20044WC2C. PMID: 34004089.

Burke AD, Apostolova L. Treatment Challenges and the Hope of Emerging Therapies in Early-Stage Alzheimer Disease. *J Clin Psychiatry.* 2021 Jun 15;82(4):BG20044AH4C. doi: 10.4088/JCP.BG20044AH4C. PMID: 34133088.

Burke AD, Goldfarb D. Facilitating Treatment Initiation in Early-Stage Alzheimer Disease. *J Clin Psychiatry.* 2022 Aug 1;83(4):LI21019DH2C. doi: 10.4088/JCP.LI21019DH2C. PMID: 35921507.

Burke AD, Goldfarb D. Timely Diagnosis of Alzheimer Disease. *J Clin Psychiatry*. 2022 Aug 1;83(4):LI21019DH1C. doi: 10.4088/JCP.LI21019DH1C. PMID: 35921505.

Burke AD. Can Emerging Therapies Resolve Unmet Needs With Current Treatment in Early-Stage Alzheimer Disease? *J Clin Psychiatry*. 2021 May 25;82(3):BG20044WC3C. doi: 10.4088/JCP.BG20044WC3C. PMID: 34033708.

Burke S, Grudzien A, Li T, Abril M, Spadola C, Barnes C, Hanson K, Grandner M, DeKosky S. Correlations between sleep disturbance and brain structures associated with neurodegeneration in the National Alzheimer's Coordinating Center Uniform Data Set. *J Clin Neurosci*. 2022 Aug 12:S0967-5868(22)00303-4. doi: 10.1016/j.jocn.2022.07.012. Epub ahead of print. PMID: 35970678.

Burns DK, Alexander RC, Welsh-Bohmer KA, Culp M, Chiang C, O'Neil J, Evans RM, Harrigan P, Plassman BL, Burke JR, Wu J, Lutz MW, Haneline S, Schwarz AJ, Schneider LS, Yaffe K, Saunders AM, Ratti E; TOMMORROW study investigators. Safety and efficacy of pioglitazone for the delay of cognitive impairment in people at risk of Alzheimer's disease (TOMMORROW): a prognostic biomarker study and a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2021 Jul;20(7):537-547. doi: 10.1016/S1474-4422(21)00043-0. PMID: 34146512

Burr P, Choudhury P. Fine Motor Disability. 2021 Oct 13. In: *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. PMID: 33085413.

Buscescu A, Choudhury P, Lee-Iannotti J, Rangan P, Shprecher D, Fantini ML, et al. Validation of a Clinical Scale for Defining RBD Severity in Participants of the North American Prodromal Synucleinopathy (NAPS) Consortium (P2-7.001). *Neurology*. 2022 May 3;98(18 Supplement):1938.

Bycura D, Santos AC, Shiffer A, Kyman S, Winfree K, Sutcliffe J, Pearson T, Sonderegger D, Cope E, Caporaso JG. Impact of Different Exercise Modalities on the Human Gut Microbiome. *Sports (Basel)*. 2021 Jan 21;9(2):14. doi: 10.3390/sports9020014. PMID: 337909775.

Cadiz MP, Jensen TD, Sens JP, Zhu K, Song WM, Zhang B, Ebbert M, Chang R, Fryer JD. Culture shock: microglial heterogeneity, activation, and disrupted single-cell microglial networks in vitro. *Mol Neurodegener*. 2022 Mar 28;17(1):26. doi: 10.1186/s13024-022-00531-1. PMID: 3528962153.

Cai S, Moutal A, Yu J, Chew LA, Isensee J, Chawla R, Gomez K, Luo S, Zhou Y, Chefdeville A, Madura C, Perez-Miller S, Bellampalli SS, Dorame A, Scott DD, François-Moutal L, Shan Z, Woodward T, Gokhale V, Hohmann AG, Vanderah TW, Patek M, Khanna M, Hucho T, Khanna R. Selective targeting of NaV1.7 via inhibition of the CRMP2-Ubc9 interaction reduces pain in rodents. *Sci Transl Med*. 2021 Nov 10;13(619):eabh1314. doi: 10.1126/scitranslmed.abh1314. Epub 2021 Nov 10. PMID: 34757807.

Cai Y, Juszczak HM, Cope EK, Goldberg AN. The microbiome in obstructive sleep apnea. *Sleep*. 2021 Aug 13;44(8):zsab061. doi: 10.1093/sleep/zsab061. PMID: 33705556.

Callister MN, Stonnington CB, Cuc A, Alcott SB, Driver-Dunckley ED, Mehta SH, Hasan S, Marks LA, Wingerchuk DM, O'Carroll CB. In Patients With Functional Movement Disorders, Is Specialized Physical Therapy Effective in Improving Motor Symptoms?: A Critically Appraised Topic. *Neurologist*. 2022 Jan 20;27(2):82-88. doi: 10.1097/NRL.0000000000000408. PMID: 35051971.

Carey SB, Lovell JT, Jenkins J, Leebens-Mack J, Schmutz J, Wilson MA, Harkess A. Representing sex chromosomes in genome assemblies. *Cell Genom*. 2022 May 11;2(5):100132. doi: 10.1016/j.xgen.2022.100132. Epub 2022 May 4. PMID: PMC9205529.

Chang R, Trushina E, Zhu K, Zaidi SSA, Lau BM, Kueider-Paisley A, Moein S, He Q, Alamprese ML, Vagnerova B, Tang A, Vijayan R, Liu Y, Saykin AJ, Brinton RD, Kaddurah-Daouk R; Alzheimer's Disease Neuroimaging Initiative† and the Alzheimer's Disease Metabolomics Consortium. Predictive metabolic networks reveal sex- and APOE genotype-specific metabolic signatures and drivers for precision medicine in Alzheimer's disease. *Alzheimers Dement*. 2022 Apr 28. doi: 10.1002/alz.12675. Epub ahead of print. PMID: 35481667.

Chatterjee K, Edmonds VS, Girardo ME, Vickers KS, Hathaway JC, Stonnington CM. Medical students describe their wellness and how to preserve it. *BMC Med Educ*. 2022 Jun 28;22(1):510. doi: 10.1186/s12909-022-03552-y. PMID: PMC9241274.

Chaudhuri, S, Fowler, MJ, Baker, C, Stopka, SA, Regan, MS, Sablatura, L, Broughton, CW, Knight, BE, Stabenfeldt, SE, Agar, NYR, Sirianni, RW*. β -cyclodextrin-poly (β -amino ester) nanoparticles are a generalizable strategy for high loading and sustained release of HDAC inhibitors. *ACS Applied Materials & Interfaces*. 2021; 13(18): 20960–20973. DOI: 10.1021/acsami.0c22587. PMID: PMC8153536.

Chen K, Guo X, Pan R, Xiong C, Harvey DJ, Chen Y, Yao L, Su Y, Reiman EM; Alzheimer's Disease Neuroimaging Initiative. Limitations of clinical trial sample size estimate by subtraction of two measurements. *Stat Med*. 2022 Mar 30;41(7):1137-1147. doi: 10.1002/sim.9244. Epub 2021 Nov 1. PMID: 34725853

Chen NK, Bell RP, Meade CS. On the down-sampling of diffusion MRI data along the angular dimension. *Magn Reson Imaging*. 2021 Oct;82:104-110. doi: 10.1016/j.mri.2021.06.012. Epub 2021 Jun 24. PMID: PMC8289744.

Chen S, Acosta D, Li L, Liang J, Chang Y, Wang C, Fitzgerald J, Morrison C, Goulbourne CN, Nakano Y, Villegas NCH, Venkataraman L, Brown C, Serrano GE, Bell E, Wemlinger T, Wu M, Kokiko-Cochran ON, Popovich P, Flowers XE, Honig LS, Vonsattel JP, Scharre DW, Beach TG, Ma Q, Kuret J, Köks S, Urano F, Duff KE, Fu H. Wolframin is a novel regulator of tau pathology and neurodegeneration. *Acta Neuropathol*. 2022 May;143(5):547-569. doi: 10.1007/s00401-022-02417-4. Epub 2022 Apr 7. PMID: 35389045.

Chen SD, Lu JY, Li HQ, Yang YX, Jiang JH, Cui M, Zuo CT, Tan L, Dong Q, Yu JT; Alzheimer's Disease Neuroimaging Initiative. Staging tau pathology with tau PET in Alzheimer's disease: a longitudinal study. *Transl Psychiatry*. 2021 Sep 18;11(1):483. doi: 10.1038/s41398-021-01602-5. PMID: 34537810

Chen X, Sun G, Tian E, Zhang M, Davtyan H, Beach TG, Reiman EM, Blurton-Jones M, Holtzman DM, Shi Y. Modeling Sporadic Alzheimer's Disease in Human Brain Organoids under Serum Exposure. *Adv Sci (Weinh)*. 2021 Sep;8(18):e2101462. doi: 10.1002/adv.202101462. Epub 2021 Aug 2. PMID: PMC8456220.

Chen YC, Ton That V, Ugonna C, Liu Y, Nadel L, Chou YH. Diffusion MRI-guided theta burst stimulation enhances memory and functional connectivity along the inferior longitudinal fasciculus in mild cognitive impairment. *Proc Natl Acad Sci U S A*. 2022 May 24;119(21):e2113778119. doi: 10.1073/pnas.2113778119. Epub 2022 May 20. PMID: PMC9173759.

Chen YC, Ton That V, Ugonna C, Liu Y, Nadel L, Chou YH. Diffusion MRI-guided theta burst stimulation enhances memory and functional connectivity along the inferior longitudinal fasciculus in mild cognitive impairment. *Proc Natl Acad Sci U S A*. 2022 May 24;119(21):e2113778119. doi: 10.1073/pnas.2113778119. Epub 2022 May 20. PMID: 35680080.

Choi G, Gin A, Su J. Optical frequency combs in aqueous and air environments at visible to near-IR wavelengths. *Opt Express*. 2022 Mar 14;30(6):8690-8699. doi: 10.1364/OE.451631. PMID: 35689704.

Chou YH, Sundman M, Ton That V, Green J, Trapani C. Cortical excitability and plasticity in Alzheimer's disease and mild cognitive impairment: A systematic review and meta-analysis of transcranial magnetic stimulation studies. *Ageing Res Rev*. 2022 Aug;79:101660. doi: 10.1016/j.arr.2022.101660. Epub 2022 Jun 6. PMID: 35680080.

Choudhury P, Graff-Radford J, Aakre JA, Wurtz L, Knopman DS, Graff-Radford NR, Kantarci K, Forsberg LK, Fields JA, Pedraza O, Chen Q, Miyagawa T, Day GS, Tipton P, Savica R, Botha H, Lachner C, Dredla B, Reichard RR, Petersen RC, Dickson DW, Boeve BF, Ferman TJ. The temporal onset of the core features in dementia with Lewy bodies. *Alzheimers Dement*. 2022 Apr;18(4):591-601. doi: 10.1002/alz.12411. Epub 2021 Nov 11. PMID: 34761850.

Choudhury P, Graff-Radford J, Aakre JA, Wurtz L, Knopman DS, Graff-Radford NR, Savica R, Kantarci K, Fields JA, Pedraza O, Reichard RR, Petersen RC, Dickson DW, Boeve BF, Ferman TJ. (2021), Evolution of core features in Lewy body disease pathologic subtypes. *Alzheimer's Dement.*, 17: e055828. <https://doi.org/10.1002/alz.055828>

Choudhury P, Ramanan VK, Boeve BF. APOE Allele Testing and Alzheimer Disease-Reply. *JAMA*. 2021 Jun 1;325(21):2211. doi: 10.1001/jama.2021.4925. PMID: 34061147.

Choudhury P, Zhang N, Shprecher D, Belden C, Goldfarb D, Shill H, Mehta S, Driver-Dunckley E, Serrano GE, Beach TG, Adler C, Atri A. (2021) Longitudinal motor decline in dementia with Lewy bodies and Parkinson's disease dementia in a community autopsy cohort. *Alzheimer's Dement.*, 17: e055838. <https://doi.org/10.1002/alz.055838>.

Chu CQ, Yu LL, Qi GY, Mi YS, Wu WQ, Lee YK, Zhai QX, Tian FW, Chen W. Can dietary patterns prevent cognitive impairment and reduce Alzheimer's disease risk: Exploring the underlying mechanisms of effects. *Neurosci Biobehav Rev*. 2022 Apr;135:104556. doi: 10.1016/j.neubiorev.2022.104556. Epub 2022 Feb 3. PMID: 35122783.

Chu M, Chen Z, Nie B, Liu L, Xie K, Cui Y, Chen K, Rosa-Neto P, Wu L. A longitudinal 18F-FDG PET/MRI study in asymptomatic stage of genetic Creutzfeldt-Jakob disease linked to G114V mutation. *J Neurol*. 2022 Jul 21. doi: 10.1007/s00415-022-11288-4. Epub ahead of print. PMID: 35864212.

Collins KL, Younis US, Tanyaratsrisakul S, Polt R, Hay M, Mansour HM, Ledford JG. Angiotensin-(1-7) Peptide Hormone Reduces Inflammation and Pathogen Burden during *Mycoplasma pneumoniae* Infection in Mice. *Pharmaceutics*. 2021 Oct 4;13(10):1614. doi: 10.3390/pharmaceutics13101614. PMID: 35689704.

Cong Z, Fu Y, Chen N, Zhang L, Yao C, Wang Y, Yao Z, Hu B. Individuals with cannabis use are associated with widespread morphological alterations in the subregions of the amygdala, hippocampus, and pallidum. *Drug Alcohol Depend*. 2022 Aug 3;239:109595. doi: 10.1016/j.drugalcdep.2022.109595. Epub ahead of print. PMID: 35961268.

Cook M, Richey A, Brafman DA, Frow EK. Weighing up the evidence used by direct-to-consumer stem cell businesses. *Stem Cell Reports*. 2021 Dec 14;16(12):2852-2860. doi: 10.1016/j.stemcr.2021.10.007. Epub 2021 Nov 11. PMID: PMC8693621.

Coon DW, Gómez-Morales A. Modifiable Risk Factors for Brain Health and Dementia and Opportunities for Intervention: A Brief Review. *Clin Gerontol*. 2022 Aug 22:1-12. doi: 10.1080/07317115.2022.2114396. Epub ahead of print. PMID: 35996225.

Cope, Emily K., Emily M. Borsom, Evan K. Bolyen, Sierra A. Jaramillo, Kathryn A. Conn, Matthew R. Dillon, Gabrielle M. Orsini, Allyson H. Hirsch, Keehoon Lee, and J. Gregory Caporaso. 2021. "Influence of Fecal Microbiota Transplantation on Gut Microbiota Composition and Neuroinflammation of 3xTg-AD Mice." *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* 17: e054648. <https://doi.org/10.1002/alz.054648> *Abstract

Crown LM, Gray DT, Schimanski LA, Barnes CA, Cowen SL. Aged Rats Exhibit Altered Behavior-Induced Oscillatory Activity, Place Cell Firing Rates, and Spatial Information Content in the CA1 Region of the Hippocampus. *J Neurosci*. 2022 Jun 1;42(22):4505-4516. doi: 10.1523/JNEUROSCI.1855-21.2022. Epub 2022 Apr 27. PMID: PMC9172068.

Cui Y, Liu Y, Yang C, Cui C, Jing D, Zhang X, Chen Y, Li B, Liang Z, Chen K, Zhang Z, Wu L. Brain structural and functional anomalies associated with simultanagnosia in patients with posterior cortical atrophy. *Brain Imaging Behav*. 2022 Jun;16(3):1148-1162. doi: 10.1007/s11682-021-00568-8. Epub 2021 Nov 17. PMID: 34787788.

Cummings JL, Ismail Z, Dickerson BC, Ballard C, Grossberg G, McEvoy B, Foff E, Atri A. Development and assessment of a brief screening tool for psychosis in dementia. *Alzheimers Dement (Amst)*. 2021 Dec 7;13(1):e12254. doi: 10.1002/dad2.12254. eCollection 2021. PMID: 34934801.

Currier Thomas T, Bromberg CE, Krishna G. Female sex in experimental traumatic brain injury research: forging a path forward. *Neural Regen Res*. 2022 Mar;17(3):550-552. doi: 10.4103/1673-5374.316602. PMID: PMC8504385.

Cutts J, Kostas W, Brafman DA. Generation of 3X FLAG-tagged human embryonic stem cell (hESC) line to study WNT-induced β -catenin DNA interactions (HVRDe009-A-2). *Stem Cell Res*. 2021 Oct 26;57:102586. doi: 10.1016/j.scr.2021.102586. Epub ahead of print. PMID: 34736039.

Das SR, Lyu X, Duong MT, Xie L, McCollum L, de Flores R, DiCalogero M, Irwin DJ, Dickerson BC, Nasrallah IM, Yushkevich PA, Wolk DA; Alzheimer's Disease Neuroimaging Initiative. Tau Atrophy Variability Reveals Phenotypic Heterogeneity in Alzheimer's Disease. *Ann Neurol*. 2021 Nov;90(5):751-762. doi: 10.1002/ana.26233. Epub 2021 Oct 15. PMID: 34617306

Dato S, Piras IS. Editorial: Omics of Human Aging and Longevity in the Post Genome Era: From Single Biomarkers to Systems Biology Approaches. *Front Genet*. 2022 May 2;13:913531. doi: 10.3389/fgene.2022.913531. PMID: PMC9108168.

DeFeis B, Ying G, Kurasz AM, DeWit L, Amofa P, Chandler M, Locke D, Shandera-Oschner A, Phatak V, Dean P, Smith G. (2021). Latent factor structure of outcome measures used in the HABIT © Mild Cognitive Impairment intervention program. *Journal of Alzheimer's Disease*. Published online 9/8/21. DOI: 10.3233/JAD-210582

Deoni SCL, Bruchhage MMK, Beauchemin J, Volpe A, D'Sa V, Huentelman M, Williams SCR. Accessible pediatric neuroimaging using a low field strength MRI scanner. *Neuroimage*. 2021 Sep;238:118273. doi: 10.1016/j.neuroimage.2021.118273. Epub 2021 Jun 17. PMID: 34146712.

Deoni SCL, Medeiros P, Deoni AT, Burton P, Beauchemin J, D'Sa V, Boskamp E, By S, McNulty C, Mileski W, Welch BE, Huentelman M. Development of a mobile low-field MRI scanner. *Sci Rep*. 2022 Apr 5;12(1):5690. doi: 10.1038/s41598-022-09760-2. PMID: 35838658.

Deshpande A, Elliott J, Kari N, Jiang B, Michel P, Toosizadeh N, Fahadan PT, Kidwell C, Wintermark M, Laksari K. Novel imaging markers for altered cerebrovascular morphology in aging, stroke, and Alzheimer's disease. *J Neuroimaging*. 2022 Jul 15. doi: 10.1111/jon.13023. Epub ahead of print. PMID: 35838658.

Dillon MR, Bolyen E, Adamov A, Belk A, Borsom E, Burcham Z, Debelius JW, Deel H, Emmons A, Estaki M, Herman C, Keefe CR, Morton JT, Oliveira RRM, Sanchez A, Simard A, Vázquez-Baeza Y, Ziemski M, Miwa HE, Kerere TA, Coote C, Bonneau R, Knight R, Oliveira G, Gopalasingam P, Kaehler BD, Cope EK, Metcalf JL, Robeson li MS, Bokulich NA, Caporaso JG. Experiences and lessons learned from two virtual, hands-on microbiome bioinformatics workshops. *PLoS Comput Biol*. 2021 Jun 24;17(6):e1009056. doi: 10.1371/journal.pcbi.1009056. PMID: 34224931.

Doppler D, Rabbani MT, Letrun R, Cruz Villarreal J, Kim DH, Gandhi S, Egatz-Gomez A, Sonker M, Chen J, Koua FHM, Yang J, Youssef M, Mazalova V, Bajt S, Shelby ML, Coleman MA, Wiedorn MO, Knoska J, Schön S, Sato T, Hunter MS, Hosseinizadeh A, Kuptiz C, Nazari R, Alvarez RC, Karpos K, Zaare S, Dobson Z, Discianno E, Zhang S, Zook JD, Bielecki J, de Wijn R, Round AR, Vagovic P, Kloos M, Vakili M, Ketawala GK, Stander NE, Olson TL, Morin K, Mondal J, Nguyen J, Meza-Aguilar JD, Kodis G, Vaiana S, Martin-Garcia JM, Mariani V, Schwander P, Schmidt M, Messerschmidt M, Ourmazd A, Zatsopin N, Weierstall U, Bruce BD, Mancuso AP, Grant T, Barty A, Chapman HN, Frank M, Fromme R, Spence JCH, Botha S, Fromme P, Kirian RA, Ros A. Co-flow injection for serial crystallography at X-ray free-electron lasers. *J Appl Crystallogr*. 2022 Feb 1;55(Pt 1):1-13. doi: 10.1107/S1600576721011079. PMID: 348805165.

Doust YV, Rowe RK, Adelson PD, Lifshitz J, Ziebell JM. Age-at-Injury Determines the Extent of Long-Term Neuropathology and Microgliosis After a Diffuse Brain Injury in Male Rats. *Front Neurol*. 2021 Sep 8;12:722526. doi: 10.3389/fneur.2021.722526. PMID: 348455817.

Duan Y, Mueller CA, Yu F, Talley KM, Shippee TP. The Relationships of Nursing Home Culture Change Practices With Resident Quality of Life and Family Satisfaction: Toward a More Nuanced Understanding. *Res Aging*. 2022 Feb;44(2):174-185. doi: 10.1177/01640275211012652. Epub 2021 May 11. PMID: 349126004.

Dugger BN, Harvey D, Beach TG, Adler CH. Peripheral tau as a biomarker for neurodegenerative diseases: is life on Earth, life on Mars? *Brain*. 2022 Aug 10;awac281. doi: 10.1093/brain/awac281. Epub ahead of print. PMID: 35947169.

Dumitrascu OM, Wang Y, Chen JJ. Clinical Machine Learning Modeling Studies: Methodology and Data Reporting. *J Neuroophthalmol*. 2022 Jun 1;42(2):145-148. doi: 10.1097/WNO.0000000000001605. Epub 2022 Apr 19. PMID: 35439230.

Duong MT, Das SR, Lyu X, Xie L, Richardson H, Xie SX, Yushkevich PA; Alzheimer's Disease Neuroimaging Initiative (ADNI), Wolk DA, Nasrallah IM. Dissociation of tau pathology and neuronal hypometabolism within the ATN framework of Alzheimer's disease. *Nat Commun.* 2022 Mar 21;13(1):1495. doi: 10.1038/s41467-022-28941-1. PMID: 35314672

Edmonds VS, Chatterjee K, Girardo ME, Butterfield RJ 3rd, Stonnington CM. Evaluation of a Novel Wellness Curriculum on Medical Student Wellbeing and Engagement Demonstrates a Need for Student-Driven Wellness Programming. *Teach Learn Med.* 2022 Feb 2:1-13. doi: 10.1080/10401334.2021.2004415. Epub ahead of print. PMID: 35107397.

Eissman JM, Dumitrescu L, Mahoney ER, Smith AN, Mukherjee S, Lee ML, Scollard P, Choi SE, Bush WS, Engelman CD, Lu Q, Fardo DW, Trittschuh EH, Mez J, Kaczorowski CC, Hernandez Saucedo H, Widaman KF, Buckley RF, Properzi MJ, Mormino EC, Yang HS, Harrison TM, Hedden T, Nho K, Andrews SJ, Tommet D, Hadad N, Sanders RE, Ruderfer DM, Gifford KA, Zhong X, Raghavan NS, Vardarajan BN; Alzheimer's Disease Neuroimaging Initiative (ADNI); Alzheimer's Disease Genetics Consortium (ADGC); A4 Study Team, Pericak-Vance MA, Farrer LA, Wang LS, Cruchaga C, Schellenberg GD, Cox NJ, Haines JL, Keene CD, Saykin AJ, Larson EB, Sperling RA, Mayeux R, Cuccaro ML, Bennett DA, Schneider JA, Crane PK, Jefferson AL, Hohman TJ. Sex differences in the genetic architecture of cognitive resilience to Alzheimer's disease. *Brain.* 2022 Jul 29;145(7):2541-2554. doi: 10.1093/brain/awac177. PMCID: PMC9337804.

Encinas-Basurto D, Konhilas JP, Polt R, Hay M, Mansour HM. Glycosylated Ang-(1-7) MasR Agonist Peptide Poly Lactic-co-Glycolic Acid (PLGA) Nanoparticles and Microparticles in Cognitive Impairment: Design, Particle Preparation, Physicochemical Characterization, and In Vitro Release. *Pharmaceutics.* 2022 Mar 8;14(3):587. doi: 10.3390/pharmaceutics14030587. PMCID: PMC8954495.

Erickson T, Malek-Ahmadi M, Luft CA, Campbell C, Strecker HK. Word Fluency Test (WFT): A parallel FAS alternative. *Appl Neuropsychol Adult.* 2022 Jan 25:1-10. doi: 10.1080/23279095.2021.2021410. Epub ahead of print. PMID: 35076309.

Fan Y, Wang G, Dong Q, Liu Y, Leporé N, Wang Y. Tetrahedral spectral feature-Based bayesian manifold learning for grey matter morphometry: Findings from the Alzheimer's disease neuroimaging initiative. *Med Image Anal.* 2021 Aug;72:102123. doi: 10.1016/j.media.2021.102123. Epub 2021 Jun 8. PMCID: PMC8316398.

Fan Y, Wang Y. Geometry-Aware Hierarchical Bayesian Learning on Manifolds. *IEEE Winter Conf Appl Comput Vis.* 2022 Jan;2022:2743-2752. doi: 10.1109/wacv51458.2022.00280. Epub 2022 Feb 15. PMCID: PMC9012487.

Farrell K, Kim S, Han N, Iida MA, Gonzalez EM, Otero-Garcia M, Walker JM, Richardson TE, Renton AE, Andrews SJ, Fulton-Howard B, Humphrey J, Vialle RA, Bowles KR, de Paiva Lopes K, Whitney K, Dangoor DK, Walsh H, Marcora E, Hefti MM, Casella A, Sissoko CT, Kapoor M, Novikova G, Udine E, Wong G, Tang W, Bhangale T, Hunkapiller J, Ayalon G, Graham RR, Cherry JD, Cortes EP, Borukov VY, McKee AC, Stein TD, Vonsattel JP, Teich AF, Gearing M, Glass J, Troncoso JC, Frosch MP, Hyman BT, Dickson DW, Murray ME, Attems J, Flanagan ME, Mao Q, Mesulam MM, Weintraub S, Woltjer RL, Pham T, Kofler J, Schneider JA, Yu L, Purohit DP, Haroutunian V, Hof PR, Gandy S, Sano M, Beach TG, Poon W, Kawas CH, Corrada MM, Rissman RA, Metcalf J, Shulberg S, Salehi B, Nelson PT, Trojanowski JQ, Lee EB, Wolk DA, McMillan CT, Keene CD, Latimer CS, Montine TJ, Kovacs GG, Lutz MI, Fischer P, Perrin RJ, Cairns NJ, Franklin EE, Cohen HT, Raj T, Cobos I, Frost B, Goate A, White III CL, Crary JF.

Genome-wide association study and functional validation implicates JADE1 in tauopathy. *Acta Neuropathol.* 2022 Jan;143(1):33-53. doi: 10.1007/s00401-021-02379-z. Epub 2021 Nov 1. PMID: PMC8786260.

Fleury J, Komnenich P, Coon DW, Volk-Craft B. Development of a Nostalgic Remembering Intervention: Feeling Safe in Dyads Receiving Palliative Care for Advanced Heart Failure. *J Cardiovasc Nurs.* 2021 May-Jun 01;36(3):221-228. doi: 10.1097/JCN.0000000000000762. PMID: PMC8041566.

Fleury J, Sedikides C, Wildschut T, Coon DW, Komnenich P. Feeling Safe and Nostalgia in Healthy Aging. *Front Psychol.* 2022 Apr 4;13:843051. doi: 10.3389/fpsyg.2022.843051. PMID: PMC9015039.

Fontenele RS, Kraberger S, Hadfield J, Driver EM, Bowes D, Holland LA, Faleye TOC, Adhikari S, Kumar R, Inchausti R, Holmes WK, Deitrick S, Brown P, Duty D, Smith T, Bhatnagar A, Yeager RA 2nd, Holm RH, von Reitzenstein NH, Wheeler E, Dixon K, Constantine T, Wilson MA, Lim ES, Jiang X, Halden RU, Scotch M, Varsani A. High-throughput sequencing of SARS-CoV-2 in wastewater provides insights into circulating variants. *Water Res.* 2021 Oct 15;205:117710. doi: 10.1016/j.watres.2021.117710. Epub 2021 Sep 25. PMID: PMC8464352.

Fox RS, Gaumont JS, Zee PC, Kaiser K, Tanner EJ, Ancoli-Israel S, Siddique J, Penedo FJ, Wu LM, Reid KJ, Parthasarathy S, Badger TA, Rini C, Ong JC. Optimizing a Behavioral Sleep Intervention for Gynecologic Cancer Survivors: Study Design and Protocol. *Front Neurosci.* 2022 Mar 4;16:818718. doi: 10.3389/fnins.2022.818718. PMID: PMC8931410.

Fox-Fuller JT, Artola A, Chen K, Pulsifer M, Ramirez D, Londono N, Aguirre- Acevedo DC, Vila-Castelar C, Baena A, Martinez J, Arboleda-Velasquez JF, Langbaum JB, Tariot PN, Reiman EM, Lopera F, Quiroz YT. Sex Differences in Cognitive Abilities Among Children With the Autosomal Dominant Alzheimer Disease Presenilin 1 E280A Variant From a Colombian Cohort. *JAMA Netw Open.* 2021 Aug 2;4(8):e2121697. doi: 10.1001/jamanetworkopen.2021.21697. PMID: PMC8408665.

Fox-Fuller JT, Torrico-Teave H, d'Oleire Uquillas F, Chen K, Su Y, Chen Y, Brickhouse M, Sanchez JS, Aguero C, Jacobs HIL, Hampton O, Guzmán-Vélez E, Vila-Castelar C, Aguirre-Acevedo DC, Baena A, Artola A, Martinez J, Pluim CF, Alvarez S, Ochoa-Escudero M, Reiman EM, Sperling RA, Lopera F, Johnson KA, Dickerson BC, Quiroz YT. Cortical thickness across the lifespan in a Colombian cohort with autosomal-dominant Alzheimer's disease: A cross-sectional study. *Alzheimers Dement (Amst).* 2021 Sep 14;13(1):e12233. doi: 10.1002/dad2.12233. eCollection 2021. PMID: 34541287

François-Moutal L, Scott DD, Ambrose AJ, Zerio CJ, Rodriguez-Sanchez M, Dissanayake K, May DG, Carlson JM, Barbieri E, Moutal A, Roux KJ, Shorter J, Khanna R, Barmada SJ, McGurk L, Khanna M. Heat shock protein Grp78/BiP/HspA5 binds directly to TDP-43 and mitigates toxicity associated with disease pathology. *Sci Rep.* 2022 May 17;12(1):8140. doi: 10.1038/s41598-022-12191-8. PMID: PMC9114370.

Freire-Cobo C, Edler MK, Varghese M, Munger E, Laffey J, Raia S, In SS, Wicinski B, Medalla M, Perez SE, Mufson EJ, Erwin JM, Guevara EE, Sherwood CC, Luebke JI, Lacreuse A, Raghanti MA, Hof PR. Comparative neuropathology in aging primates: A perspective. *Am J Primatol.* 2021 Nov;83(11):e23299. doi: 10.1002/ajp.23299. Epub 2021 Jul 13. PMID: PMC8551009.

Furlong MA, Alexander GE, Klimentidis YC, Raichlen DA. Association of Air Pollution and Physical Activity With Brain Volumes. *Neurology*. 2021 Dec 8;98(4):e416–26. doi: 10.1212/WNL.0000000000013031. Epub ahead of print. PMID: PMC8793107.

Galaz Z, Drotar P, Mekyska J, Gazda M, Mucha J, Zvoncak V, Smekal Z, Faundez-Zanuy M, Castrillon R, Orozco-Aroyave JR, Rapcsak S, Kincses T, Brabenec L, Rektorova I. Comparison of CNN-Learned vs. Handcrafted Features for Detection of Parkinson's Disease Dysgraphia in a Multilingual Dataset. *Front Neuroinform*. 2022 May 30;16:877139. doi: 10.3389/fninf.2022.877139. PMID: PMC9198652.

Ganos C, Sarva H, Kurvits L, Gilbert DL, Hartmann A, Worbe Y, Mir P, Müller-Vahl KR, Münchau A, Shprecher D, Singer HS, Deeb W, Okun MS, Malaty IA, Hallett M, Tijssen MA, Pringsheim T, Martino D; Tic Disorders and Tourette Syndrome Study Group of the International Parkinson and Movement Disorder Society. Clinical Practice Patterns in Tic Disorders Among Movement Disorder Society Members. *Tremor Other Hyperkinet Mov (N Y)*. 2021 Oct 28;11:43. doi: 10.5334/tohm.656. eCollection 2021. PMID: 34754602

Gates C, Ananyev G, Roy-Chowdhury S, Cullinane B, Miller M, Fromme P, Dismukes GC. Why Did Nature Choose Manganese over Cobalt to Make Oxygen Photosynthetically on the Earth? *J Phys Chem B*. 2022 May 5;126(17):3257–3268. doi: 10.1021/acs.jpcc.2c00749. Epub 2022 Apr 21. PMID: 35446582.

Geda YE, Krell-Roesch J, Fisseha Y, Tefera A, Beyero T, Rosenbaum D, Szabo TG, Araya M, Hayes SC. Acceptance and Commitment Therapy in a Low-Income Country in Sub-Saharan Africa: A Call for Further Research. *Front Public Health*. 2021 Sep 23;9:732800. doi: 10.3389/fpubh.2021.732800. PMID: PMC8494766.

Gergelis KR, Anand US, Rian JS, Roberts KW, Quinones PJ, Olivier KR, Corbin KS, Stonnington CM. Integrating a Grassroots Well-Being Curriculum into a Radiation Oncology Residency Program. *Adv Radiat Oncol*. 2021 Oct 27;7(1):100837. doi: 10.1016/j.adro.2021.100837. PMID: PMC8654639.

Ghani SB, Delgadillo ME, Granados K, Okuagu AC, Wills CCA, Alfonso-Miller P, Buxton OM, Patel SR, Ruiz J, Parthasarathy S, Haynes PL, Molina P, Seixas A, Jean-Louis G, Grandner MA. Patterns of Eating Associated with Sleep Characteristics: A Pilot Study among Individuals of Mexican Descent at the US-Mexico Border. *Behav Sleep Med*. 2022 Mar-Apr;20(2):212–223. doi: 10.1080/15402002.2021.1902814. Epub 2021 Mar 31. PMID: PMC8481352.

Gialluisi A, Reccia MG, Modugno N, Nutile T, Lombardi A, Di Giovannantonio LG, Pietracupa S, Ruggiero D, Scala S, Gambardella S; International Parkinson's Disease Genomics Consortium (IPDGC), Iacoviello L, Gianfrancesco F, Acampora D, D'Esposito M, Simeone A, Ciullo M, Esposito T. Identification of sixteen novel candidate genes for late onset Parkinson's disease. *Mol Neurodegener*. 2021 Jun 21;16(1):35. doi: 10.1186/s13024-021-00455-2. PMID: PMC8215754.

Giordano KR, Law LM, Henderson J, Rowe RK, Lifshitz J. Time Course of Remote Neuropathology Following Diffuse Traumatic Brain Injury in the Male Rat. *Exp Neurol*. 2022 Apr 30;31(2):105–115. doi: 10.5607/en21027. PMID: PMC9194637.

Giordano, KR, CR Denman, PS Dubisch, M Akhter, J Lifshitz. (2021) An Update on the Rod Microglia Variant in Experimental and Clinical Brain Injury and Disease. *Brain Communications* 3(1):fcaa227 PMID: 33501429 <https://doi.org/10.1093/braincomms/fcaa227> **Journal Cover Image

Giordano, KR, LM Law, J Henderson, RK Rowe, J Lifshitz. (2022) Neuropathology Following Diffuse Traumatic Brain Injury in the Rat. *Experimental Neurobiology* 31(2):105-115 PMID: 35673999. <https://doi.org/10.5607/en21027>

Glisky EL, Woolverton CB, McVeigh KS, Grilli MD. Episodic Memory and Executive Function Are Differentially Affected by Retests but Similarly Affected by Age in a Longitudinal Study of Normally-Aging Older Adults. *Front Aging Neurosci.* 2022 Apr 13;14:863942. doi: 10.3389/fnagi.2022.863942. PMID: PMC9043807.

Goddard JA, Petersen SC, Call GB, Chaston JM. Genome Sequence of *Acetobacter tropicalis* DmPark25_167, a Bacterium Isolated from a *Drosophila melanogaster* Genetic Model of Parkinson's Disease. *Microbiol Resour Announc.* 2021 Jan 7;10(1):e01138-20. doi: 10.1128/MRA.01138-20. PMID: PMC8407700.

Goldfarb D, Allen AM, Nisson LE, Petitti DB, Saner D, Langford C, Burke WJ, Reiman EM, Atri A, Tariot PN. Design and Development of a Community-Based, Interdisciplinary, Collaborative Dementia Care Program. *Am J Geriatr Psychiatry.* 2022 Jun;30(6):651-660. doi: 10.1016/j.jagp.2021.10.014. Epub 2021 Nov 12. PMID: 34893448

Gonneaud J, Baria AT, Pichet Binette A, Gordon BA, Chhatwal JP, Cruchaga C, Jucker M, Levin J, Salloway S, Farlow M, Gauthier S, Benzinger TLS, Morris JC, Bateman RJ, Breitner JCS, Poirier J, Vachon-Preseu E, Villeneuve S; Alzheimer's Disease Neuroimaging Initiative (ADNI); Dominantly Inherited Alzheimer Network (DIAN) Study Group; Pre-symptomatic Evaluation of Experimental or Novel Treatments for Alzheimer's Disease (PREVENT-AD) Research Group. Accelerated functional brain aging in pre-clinical familial Alzheimer's disease. *Nat Commun.* 2021 Sep 9;12(1):5346. doi: 10.1038/s41467-021-25492-9. PMID: 34504080

Graves LV, Churchill EG, Williams ME, Van Etten EJ, Bondi MW, Salmon DP, Corey-Bloom J, Delis DC, Gilbert PE. Source recognition discriminability impairment in Huntington's versus Alzheimer's disease: Evidence from the CVLT-3. *Appl Neuropsychol Adult.* 2022 Aug 19:1-6. doi: 10.1080/23279095.2022.2112682. Epub ahead of print. PMID: 35984776.

Green JM, Sundman MH, Chou YH. Opioid-induced microglia reactivity modulates opioid reward, analgesia, and behavior. *Neurosci Biobehav Rev.* 2022 Apr;135:104544. doi: 10.1016/j.neubiorev.2022.104544. Epub 2022 Jan 25. PMID: 35090951.

Greimel S, Wyman JF, Zhang L, Yu F. Recruitment and Screening Methods in Alzheimer's Disease Research: The FIT-AD Trial. *J Gerontol A Biol Sci Med Sci.* 2022 Mar 3;77(3):547-553. doi: 10.1093/gerona/glab092. PMID: PMC8893175.

Griffiths DR, Law LM, Young C, Fuentes A, Truran S, Karamanova N, Bell LC, Turner G, Emerson H, Mastroeni D, Gonzales R, Reaven PD, Quarles CC, Migrino RQ, Lifshitz J. Chronic Cognitive and Cerebrovascular Function Following Mild Traumatic Brain Injury in Rats. *J Neurotrauma.* 2022 May 20. doi: 10.1089/neu.2022.0015. Epub ahead of print. PMID: 35593008.

Grilli MD, McVeigh KS, Hakim ZM, Wank AA, Getz SJ, Levin BE, Ebner NC, Wilson RC. Is This Phishing? Older Age Is Associated With Greater Difficulty Discriminating Between Safe and Malicious Emails. *J Gerontol B Psychol Sci Soc Sci.* 2021 Oct 30;76(9):1711-1715. doi: 10.1093/geronb/gbaa228. PMID: PMC8557838.

Guo X, Chen K, Chen Y, Xiong C, Su Y, Yao L, Reiman EM. A computational Monte Carlo simulation strategy to determine the temporal ordering of abnormal age onset among biomarkers of Alzheimers disease. *IEEE/ACM Trans Comput Biol Bioinform.* 2021 Aug 24;PP. doi: 10.1109/TCBB.2021.3106939. Online ahead of print. PMID: 34428151

Gust CJ, Moe EN, Seals DR, Banich MT, Andrews-Hanna JR, Hutchison KE, Bryan AD. Associations Between Age and Resting State Connectivity Are Partially Dependent Upon Cardiovascular Fitness. *Front Aging Neurosci.* 2022 Apr 20;14:858405. doi: 10.3389/fnagi.2022.858405. PMID: PMC9067399.

Hall S, Orrù CD, Serrano GE, Galasko D, Hughson AG, Groveman BR, Adler CH, Beach TG, Caughey B, Hansson O. Performance of α Synuclein RT-QuIC in relation to neuropathological staging of Lewy body disease. *Acta Neuropathol Commun.* 2022 Jun 22;10(1):90. doi: 10.1186/s40478-022-01388-7. PMID: PMC9219141.

Hardcastle C, Hausman HK, Kraft JN, Albizu A, Evangelista ND, Boutzoukas EM, O'Shea A, Langer K, Van Van Etten E, Bharadwaj PK, Song H, Smith SG, Porges E, DeKosky ST, Hishaw GA, Wu SS, Marsiske M, Cohen R, Alexander GE, Woods AJ. Higher-order resting state network association with the useful field of view task in older adults. *Geroscience.* 2022 Feb;44(1):131-145. doi: 10.1007/s11357-021-00441-y. Epub 2021 Aug 25. PMID: PMC8810967.

Hardcastle C, Hausman HK, Kraft JN, Albizu A, O'Shea A, Boutzoukas EM, Evangelista ND, Langer K, Van Etten EJ, Bharadwaj PK, Song H, Smith SG, Porges E, DeKosky ST, Hishaw GA, Wu SS, Marsiske M, Cohen R, Alexander GE, Woods AJ. Proximal improvement and higher-order resting state network change after multidomain cognitive training intervention in healthy older adults. *Geroscience.* 2022 Apr;44(2):1011-1027. doi: 10.1007/s11357-022-00535-1. Epub 2022 Mar 8. PMID: PMC9135928.

Harerimana NV, Liu Y, Gerasimov ES, Duong D, Beach TG, Reiman EM, Schneider JA, Boyle P, Lori A, Bennett DA, Lah JJ, Levey AI, Seyfried NT, Wingo TS, Wingo AP. Genetic Evidence Supporting a Causal Role of Depression in Alzheimer's Disease. *Biol Psychiatry.* 2022 Jul 1;92(1):25-33. doi: 10.1016/j.biopsych.2021.11.025. Epub 2021 Dec 16. PMID: PMC9200901.

Hart CM, Mills C, Thiemann RF, Andrews-Hanna JR, Tomfohr-Madsen L, Kam JWY. Task-unrelated thought increases after consumption of COVID-19 and general news. *Cogn Res Princ Implic.* 2022 Jul 25;7(1):69. doi: 10.1186/s41235-022-00420-7. PMID: 35876968; PMID: PMC9309453.

Hartlage-Rübsamen M, Bluhm A, Mocerri S, Machner L, Köppen J, Schenk M, Hilbrich I, Holzer M, Weidenfeller M, Richter F, Coras R, Serrano GE, Beach TG, Schilling S, von Hörsten S, Xiang W, Schulze A, Roßner S. A glutaminy cyclase-catalyzed α -synuclein modification identified in human synucleinopathies. *Acta Neuropathol.* 2021 Sep;142(3):399-421. doi: 10.1007/s00401-021-02349-5. Epub 2021 Jul 26. PMID: 34309760

Hatton C, Ghanem SS, Koss DJ, Abdi IY, Gibbons E, Guerreiro R, Bras J; International DLB Genetics Consortium, Walker L, Gelpi E, Heywood W, Outeiro TF, Attems J, McFarland R, Forsyth R, El-Agnaf OM, Erskine D. Prion-like α -synuclein pathology in the brain of infants with Krabbe disease. *Brain.* 2022 May 24;145(4):1257-1263. doi: 10.1093/brain/awac002. PMID: PMC9128812.

Haugg A, Renz FM, Nicholson AA, Lor C, Götzendorfer SJ, Sladky R, Skouras S, McDonald A, Craddock C, Hellrung L, Kirschner M, Herdener M, Koush Y, Papoutsi M, Keynan J, Hendler T, Cohen Kadosh K, Zich C, Kohl SH, Hallschmid M, MacInnes J, Adcock RA, Dickerson KC, Chen NK, Young K, Bodurka J, Marxen M, Yao S, Becker B, Auer T, Schweizer R, Pamplona G, Lanius RA, Emmert K, Haller S, Van De Ville D, Kim DY, Lee JH, Marins T, Megumi F, Sorger B, Kamp T, Liew SL, Veit R, Spetter M, Weiskopf N, Scharnowski F, Steyrl D. Predictors of real-time fMRI neurofeedback performance and improvement - A machine learning mega-analysis. *Neuroimage*. 2021 Aug 15;237:118207. doi: 10.1016/j.neuroimage.2021.118207. Epub 2021 May 25. PMID: 34048901.

Hausman HK, Hardcastle C, Albizu A, Kraft JN, Evangelista ND, Boutzoukas EM, Langer K, O'Shea A, Van Etten EJ, Bharadwaj PK, Song H, Smith SG, Porges E, DeKosky ST, Hishaw GA, Wu S, Marsiske M, Cohen R, Alexander GE, Woods AJ. Cingulo-opercular and frontoparietal control network connectivity and executive functioning in older adults. *Geroscience*. 2022 Apr;44(2):847-866. doi: 10.1007/s11357-021-00503-1. Epub 2021 Dec 23. PMC9135913.

Hay M, Ryan L, Huentelman M, Konhilas J, Hoyer-Kimura C, Beach TG, Serrano GE, Reiman EM, Blennow K, Zetterberg H, Parthasarathy S. Serum Neurofilament Light is elevated in COVID-19 Positive Adults in the ICU and is associated with Co-Morbid Cardiovascular Disease, Neurological Complications, and Acuity of Illness. *Cardiol Cardiovasc Med*. 2021 Oct;5(5):551-565. doi: 10.26502/fccm.92920221. Epub 2021 Oct 13. PMCID: PMC8547787.

Heath L, Earls JC, Magis AT, Kornilov SA, Lovejoy JC, Funk CC, Rappaport N, Logsdon BA, Mangravite LM, Kunkle BW, Martin ER, Naj AC, Ertekin-Taner N, Golde TE, Hood L, Price ND; Alzheimer's Disease Genetics Consortium. Manifestations of Alzheimer's disease genetic risk in the blood are evident in a multiomic analysis in healthy adults aged 18 to 90. *Sci Rep*. 2022 Apr 12;12(1):6117. doi: 10.1038/s41598-022-09825-2. PMCID: PMC9005657.

Helboe L, Rosenqvist N, Volbracht C, Pedersen LØ, Pedersen JT, Christensen S, Egebjerg J, Christoffersen CT, Bang-Andersen B, Beach TG, Serrano GE, Falsig J. Highly Specific and Sensitive Target Binding by the Humanized pS396-Tau Antibody hC10.2 Across a Wide Spectrum of Alzheimer's Disease and Primary Tauopathy Postmortem Brains. *J Alzheimers Dis*. 2022;88(1):207-228. doi: 10.3233/JAD-220125. PMID: 35570492.

Henderson AR, Wang Q, Meechoovet B, Siniard AL, Naymik M, De Both M, Huentelman MJ, Caselli RJ, Driver-Dunckley E, Dunckley T. DNA Methylation and Expression Profiles of Whole Blood in Parkinson's Disease. *Front Genet*. 2021; 12:640266 Epub 2021 Apr 26 PMCID: 8107387 DOI: 10.3389/fgene.2021.640266

Hendrix JA, Airey DC, Britton A, Burke AD, Capone GT, Chavez R, Chen J, Chicoine B, Costa ACS, Dage JL, Doran E, Esbensen A, Evans CL, Faber KM, Foroud TM, Hart S, Haugen K, Head E, Hendrix S, Hillerstrom H, Kishnani PS, Krell K, Ledesma DL, Lai F, Lott I, Ochoa-Lubinoff C, Mason J, Nicodemus-Johnson J, Proctor NK, Pulsifer MB, Revta C, Rosas HD, Rosser TC, Santoro S, Schafer K, Scheidemantel T, Schmitt F, Skotko BG, Stasko MR, Talboy A, Torres A, Wilmes K, Woodward J, Zimmer JA, Feldman HH, Mobley W. Cross-Sectional Exploration of Plasma Biomarkers of Alzheimer's Disease in Down Syndrome: Early Data from the Longitudinal Investigation for Enhancing Down Syndrome Research (LIFE-DSR) Study. *J Clin Med*. 2021 Apr 28;10(9):1907. doi: 10.3390/jcm10091907. PMCID: PMC8124643.

Hooyman A, Lingo VanGilder J, Schaefer SY. Mediation Analysis of the Effect of Visuospatial Memory on Motor Skill Learning in Older Adults. *J Mot Behav*. 2022 Jul 28:1-10. doi: 10.1080/00222895.2022.2105793. Epub ahead of print. PMID: 35902117.

Hooyman A, Talboom JS, DeBoth MD, Ryan L, Huentelman MJ, Schaefer SY. Remote, Unsupervised Functional Motor Task Evaluation in Older Adults across the United States Using the MindCrowd Electronic Cohort. *Dev Neuropsychol*. 2021 Sep;46(6):435-446. doi: 10.1080/87565641.2021.1979005. Epub 2021 Oct 6. PMID: 34617021.

Hoyer-Kimura C, Konhilas JP, Mansour HM, Polt R, Doyle KP, Billheimer D, Hay M. Neurofilament light: a possible prognostic biomarker for treatment of vascular contributions to cognitive impairment and dementia. *J Neuroinflammation*. 2021 Oct 15;18(1):236. doi: 10.1186/s12974-021-02281-1. PMID: 34617021.

Huang W, Li X, Li H, Wang W, Chen K, Xu K, Zhang J, Chen Y, Wei D, Shu N, Zhang Z. Accelerated Brain Aging in Amnesic Mild Cognitive Impairment: Relationships with Individual Cognitive Decline, Risk Factors for Alzheimer Disease, and Clinical Progression. *Radiol Artif Intell*. 2021 Jun 23;3(5):e200171. doi: 10.1148/ryai.2021200171. eCollection 2021 Sep. PMID: 34617021

Huang X, Zhao X, Li B, Cai Y, Zhang S, Wan Q, Yu F. Comparative efficacy of various exercise interventions on cognitive function in patients with mild cognitive impairment or dementia: A systematic review and network meta-analysis. *J Sport Health Sci*. 2022 Mar;11(2):212-223. doi: 10.1016/j.jshs.2021.05.003. Epub 2021 May 16. PMID: 34617021.

Huang X, Zhao X, Li B, Cai Y, Zhang S, Yu F, Wan Q. Biomarkers for evaluating the effects of exercise interventions in patients with MCI or dementia: A systematic review and meta-analysis. *Exp Gerontol*. 2021 Aug;151:111424. doi: 10.1016/j.exger.2021.111424. Epub 2021 May 26. PMID: 34051283.

Hutchins E, Reiman R, Winarta J, Beecroft T, Richholt R, De Both M, Shahbender K, Carlson E, Janss A, Siniard A, Balak C, Bruhns R, Whitsett TG, McCoy R, Anastasi M, Allen A, Churas B, Huentelman M, Van Keuren-Jensen K. Extracellular circular RNA profiles in plasma and urine of healthy, male college athletes. *Sci Data*. 2021 Oct 28;8(1):276. doi: 10.1038/s41597-021-01056-w. PMID: 34617021.

Hutchinson E, Osting S, Rutecki P, Sutula T. Diffusion Tensor Orientation as a Microstructural MRI Marker of Mossy Fiber Sprouting After TBI in Rats. *J Neuropathol Exp Neurol*. 2022 Jan 21;81(1):27-47. doi: 10.1093/jnen/nlab123. PMID: 34865073.

Hutchinson EB, Romero-Lozano A, Johnson HR, Knutsen AK, Bosomtwi A, Korotcov A, Shunmugavel A, King SG, Schwerin SC, Juliano SL, Dardzinski BJ, Pierpaoli C. Translationally Relevant Magnetic Resonance Imaging Markers in a Ferret Model of Closed Head Injury. *Front Neurosci*. 2022 Feb 23;15:779533. doi: 10.3389/fnins.2021.779533. PMID: 34617021.

Ignacio M, Oesterle S, Mercado M, Carver A, Lopez G, Wolfersteig W, Ayers S, Ki S, Hamm K, Parthasarathy S, Berryhill A, Evans L, Sabo S, Doubeni C. Narratives from African American/Black, American Indian/Alaska Native, and Hispanic/Latinx community members in Arizona to enhance COVID-19 vaccine and vaccination uptake. *J Behav Med*. 2022 Mar 24:1-13. doi: 10.1007/s10865-022-00300-x. Epub ahead of print. PMID: 34617021.

Inglese M, Patel N, Linton-Reid K, Loreto F, Win Z, Perry RJ, Carswell C, Grech-Sollars M, Crum WR, Lu H, Malhotra PA; Alzheimer's Disease Neuroimaging Initiative, Aboagye EO. A predictive model using the mesoscopic architecture of the living brain to detect Alzheimer's disease. *Commun Med (Lond)*. 2022 Jun 20;2:70. doi: 10.1038/s43856-022-00133-4. eCollection 2022. PMID: 35759330

Iwanski J, Kazmouz SG, Li S, Stansfield B, Salem TT, Perez-Miller S, Kazui T, Jena L, Uhrlaub JL, Lick S, Nikolich-Zugich J, Konhilas JP, Gregorio CC, Khanna M, Campos SK, Churko JM. Antihypertensive drug treatment and susceptibility to SARS-CoV-2 infection in human PSC-derived cardiomyocytes and primary endothelial cells. *Stem Cell Reports*. 2021 Oct 12;16(10):2459-2472. doi: 10.1016/j.stemcr.2021.08.018. Epub 2021 Sep 1. PMID: PMC8407952.

Izadi A, Schedlbauer A, Ondek K, Disse G, Ekstrom AD, Cowen SL, Shahlaie K, Gurkoff GG. Early Intervention via Stimulation of the Medial Septal Nucleus Improves Cognition and Alters Markers of Epileptogenesis in Pilocarpine-Induced Epilepsy. *Front Neurol*. 2021 Sep 7;12:708957. doi: 10.3389/fneur.2021.708957. PMID: PMC8452867.

Jansen WJ, Janssen O, Tijms BM, Vos SJB, Ossenkuppele R, Visser PJ; Amyloid Biomarker Study Group, Aarsland D, Alcolea D, Altomare D, von Arnim C, Baiardi S, Baldeiras I, Barthel H, Bateman RJ, Van Berckel B, Binette AP, Blennow K, Boada M, Boecker H, Bottlaender M, den Braber A, Brooks DJ, Van Buchem MA, Camus V, Carill JM, Cerman J, Chen K, Chételat G, Chipi E, Cohen AD, Daniels A, Delarue M, Didic M, Drzezga A, Dubois B, Eckerström M, Ekblad LL, Engelborghs S, Epelbaum S, Fagan AM, Fan Y, Fladby T, Fleisher AS, Van der Flier WM, Förster S, Fortea J, Frederiksen KS, Freund-Levi Y, Frings L, Frisoni GB, Fröhlich L, Gabryelewicz T, Gertz HJ, Gill KD, Gkatzima O, Gómez-Tortosa E, Grimmer T, Guedj E, Habeck CG, Hampel H, Handels R, Hansson O, Hausner L, Hellwig S, Heneka MT, Herukka SK, Hildebrandt H, Hodges J, Hort J, Huang CC, Iriondo AJ, Itoh Y, Ivanoiu A, Jagust WJ, Jessen F, Johannsen P, Johnson KA, Kandimalla R, Kapaki EN, Kern S, Kilander L, Klimkiewicz-Mrowiec A, Klunk WE, Koglin N, Kornhuber J, Kramberger MG, Kuo HC, Van Laere K, Landau SM, Landeau B, Lee DY, de Leon M, Leyton CE, Lin KJ, Lleó A, Löwenmark M, Madsen K, Maier W, Marcusson J, Marquié M, Martinez-Lage P, Maserejian N, Mattsson N, de Mendonça A, Meyer PT, Miller BL, Minatani S, Mintun MA, Mok VCT, Molinuevo JL, Morbelli SD, Morris JC, Mroczko B, Na DL, Newberg A, Nobili F, Nordberg A, Olde Rikkert MGM, de Oliveira CR, Olivieri P, Orellana A, Paraskevas G, Parchi P, Pardini M, Parnetti L, Peters O, Poirier J, Popp J, Prabhakar S, Rabinovici GD, Ramakers IH, Rami L, Reiman EM, Rinne JO, Rodrigue KM, Rodríguez-Rodríguez E, Roe CM, Rosa-Neto P, Rosen HJ, Rot U, Rowe CC, Rütther E, Ruiz A, Sabri O, Sakhardande J, Sánchez-Juan P, Sando SB, Santana I, Sarazin M, Scheltens P, Schröder J, Selnes P, Seo SW, Silva D, Skoog I, Snyder PJ, Soininen H, Sollberger M, Sperling RA, Spuru L, Stern Y, Stomrud E, Takeda A, Teichmann M, Teunissen CE, Thompson LI, Tomassen J, Tsolaki M, Vandenberghe R, Verbeek MM, Verhey FRJ, Villemagne V, Villeneuve S, Vogelgsang J, Waldemar G, Wallin A, Wallin ÅK, Wiltfang J, Wolk DA, Yen TC, Zboch M, Zetterberg H. Prevalence Estimates of Amyloid Abnormality Across the Alzheimer Disease Clinical Spectrum. *JAMA Neurol*. 2022 Mar 1;79(3):228-243. doi: 10.1001/jamaneurol.2021.5216. PMID: 35099509

Jasbi P, Shi X, Chu P, Elliott N, Hudson H, Jones D, Serrano G, Chow B, Beach TG, Liu L, Jentarra G, Gu H. Metabolic Profiling of Neocortical Tissue Discriminates Alzheimer's Disease from Mild Cognitive Impairment, High Pathology Controls, and Normal Controls. *J Proteome Res*. 2021 Sep 3;20(9):4303-4317. doi: 10.1021/acs.jproteome.1c00290. Epub 2021 Aug 6. PMID: 34355917.

Jebahi, F^o., Nickels, K.V^o., Kielar, A. Predicting Confrontation Naming in the Logopenic Variant of Primary Progressive Aphasia (under review). medRxiv 2022.06.25.22276804; doi: <https://doi.org/10.1101/2022.06.25.2227680>

Jett S, Malviya N, Schelbaum E, Jang G, Jahan E, Clancy K, Hristov H, Pahlajani S, Niotis K, Loeb-Zeitlin S, Havryliuk Y, Isaacson R, Brinton RD, Mosconi L. Endogenous and Exogenous Estrogen Exposures: How Women's Reproductive Health Can Drive Brain Aging and Inform Alzheimer's Prevention. *Front Aging Neurosci.* 2022 Mar 9;14:831807. doi: 10.3389/fnagi.2022.831807. PMID: 35581512.

Jett S, Schelbaum E, Jang G, Boneu Yopez C, Dyke JP, Pahlajani S, Diaz Brinton R, Mosconi L. Ovarian steroid hormones: A long overlooked but critical contributor to brain aging and Alzheimer's disease. *Front Aging Neurosci.* 2022 Jul 19;14:948219. doi: 10.3389/fnagi.2022.948219. PMID: 35581512.

Jiang J, Sheng C, Chen G, Liu C, Jin S, Li L, Jiang X, Han Y; Alzheimer's Disease Neuroimaging Initiative. Glucose metabolism patterns: A potential index to characterize brain ageing and predict high conversion risk into cognitive impairment. *Geroscience.* 2022 May 18. doi: 10.1007/s11357-022-00588-2. Online ahead of print. PMID: 35581512

Johnson ECB, Carter EK, Dammer EB, Duong DM, Gerasimov ES, Liu Y, Liu J, Betarbet R, Ping L, Yin L, Serrano GE, Beach TG, Peng J, De Jager PL, Haroutunian V, Zhang B, Gaiteri C, Bennett DA, Gearing M, Wingo TS, Wingo AP, Lah JJ, Levey AI, Seyfried NT. Large-scale deep multi-layer analysis of Alzheimer's disease brain reveals strong proteomic disease-related changes not observed at the RNA level. *Nat Neurosci.* 2022 Feb;25(2):213-225. doi: 10.1038/s41593-021-00999-y. Epub 2022 Feb 3. PMID: 35115731

Joseph RP, Pituch KA, Guest MA, Maxfield M, Peckham A, Coon DW, Kim W, Langer SS. Physical activity among predominantly white middle-aged and older US adults during the SARS-CoV-2 pandemic: Results from a national longitudinal survey. *Frontiers in Public Health.* 2021 Apr 13;9:652197. DOI: 10.3389/fpubh.2021.652197 PMID: 34076643.

Julayanont P, Wicklund M. Frontotemporal Dementia and the Sagging Brain. *Neurology.* 2022 May 10;98(19):786-787. doi: 10.1212/WNL.0000000000200613. Epub 2022 Mar 25. PMID: 35338073.

Jun GR, You Y, Zhu C, Meng G, Chung J, Panitch R, Hu J, Xia W; Alzheimer's Disease Genetics Consortium, Bennett DA, Foroud TM, Wang LS, Haines JL, Mayeux R, Pericak-Vance MA, Schellenberg GD, Au R, Lunetta KL, Ikezu T, Stein TD, Farrer LA. Protein phosphatase 2A and complement component 4 are linked to the protective effect of APOE ϵ 2 for Alzheimer's disease. *Alzheimers Dement.* 2022 Feb 9;10.1002/alz.12607. doi: 10.1002/alz.12607. Epub ahead of print. PMID: 35360190.

Jutten RJ, Papp KV, Hendrix S, Ellison N, Langbaum JB, Donohue MC, Hassenstab J, Maruff P, Rentz DM, Harrison J, Cummings J, Scheltens P, Sikkes SAM. Why a clinical trial is as good as its outcome measure: A framework for the selection and use of cognitive outcome measures for clinical trials of Alzheimer's disease. *Alzheimers Dement.* 2022 Sep 10. doi: 10.1002/alz.12773. Epub ahead of print. PMID: 36086926.

Kaivola K, Shah Z, Chia R; International LBD Genomics Consortium, Scholz SW. Genetic evaluation of dementia with Lewy bodies implicates distinct disease subgroups. *Brain.* 2022 Jun 3;145(5):1757-1762. doi: 10.1093/brain/awab402. PMID: 35381062

Kamali A, Dieckhaus L, Peters EC, Preszler CA, Witte RS, Pires PW, Hutchinson EB, Laksari K. Hyperacute pathophysiology of traumatic and vascular brain injury captured by ultrasound, photoacoustic, and magnetic resonance imaging. arXiv preprint arXiv:2202.12268. 2022 Feb 24 <https://doi.org/10.48550/arXiv.2202.12268>

Kelley CM, Ginsberg SD, Liang WS, Counts SE, Mufson EJ. Posterior cingulate cortex reveals an expression profile of resilience in cognitively intact elders. *Brain Commun.* 2022 Jun 21;4(4):fcac162. doi: 10.1093/braincomms/fcac162. PMID: PMC9263888.

Khayoun R, Devick KL, Chandler MJ, Shandera-Ochsner AL, De Wit L, Cuc A, Smith GE, Locke DEC. The impact of patient and partner personality traits on learning success for a cognitive rehabilitation intervention for patients with MCI. *Neuropsychol Rehabil.* 2021 Jul 7:1-13. doi: 10.1080/09602011.2021.1948872. Epub ahead of print. PMID: 34232113.

Khokhriakov I, Merkulova O, Nozik A, Fromme P, Mazalova V. A novel solution for controlling hardware components of accelerators and beamlines. *J Synchrotron Radiat.* 2022 May 1;29(Pt 3):644-653. doi: 10.1107/S1600577522002685. Epub 2022 Apr 4.: PMID: PMC9070715.

Kielar A, Patterson D, Chou YH. Efficacy of repetitive transcranial magnetic stimulation in treating stroke aphasia: Systematic review and meta-analysis. *Clin Neurophysiol.* 2022 Aug;140:196-227. doi: 10.1016/j.clinph.2022.04.017. Epub 2022 May 5. PMID: 35606322.

Kielar A, Shah-Basak PP, Patterson DK, Jokel R, Meltzer JA. Electrophysiological abnormalities as indicators of early-stage pathology in Primary Progressive Aphasia (PPA): A case study in semantic variant PPA. *Neurocase.* 2022 Feb;28(1):110-122. doi: 10.1080/13554794.2022.2039207. Epub 2022 Mar 1. PMID: 35230912.

Kim B, Andrews-Hanna JR, Han J, Lee E, Woo CW. When self comes to a wandering mind: Brain representations and dynamics of self-generated concepts in spontaneous thought. *Sci Adv.* 2022 Sep 2;8(35):eabn8616. doi: 10.1126/sciadv.abn8616. Epub 2022 Aug 31. PMID: 36044582.

Kim YJ, Brinton RD. Precision hormone therapy: identification of positive responders. *Climacteric.* 2021 Aug;24(4):350-358. doi: 10.1080/13697137.2021.1882418. Epub 2021 Feb 22. PMID: PMC8989059.

Kishimoto AO, Kishimoto Y, Shi X, Hutchinson EB, Zhang H, Shi Y, Oliveira G, Li L, Welham NV, Rowland IJ. High-resolution magnetic resonance and mass spectrometry imaging of the human larynx. *J Anat.* 2021 Sep;239(3):545-556. doi: 10.1111/joa.13451. Epub 2021 May 25. PMID: PMC8349453.

Klimentidis YC, Newell M, VAN DER Zee MD, Bland VL, May-Wilson S, Arani G, Menni C, Mangino M, Arora A, Raichlen DA, Alexander GE, Wilson JF, Boomsma DI, Hottenga JJ, DE Geus EJC, Pirastu N. Genome-wide Association Study of Liking for Several Types of Physical Activity in the UK Biobank and Two Replication Cohorts. *Med Sci Sports Exerc.* 2022 Aug 1;54(8):1252-1260. doi: 10.1249/MSS.0000000000002907. Epub 2022 Mar 11. PMID: PMC9288543.

Knittel J, Srinivasan G, Frisch C, Brookhouser N, Raman S, Essuman A, Brafman DA. A microcarrier-based protocol for scalable generation and purification of human induced pluripotent stem cell-derived neurons and astrocytes. *STAR Protoc.* 2022 Aug 18;3(3):101632. doi: 10.1016/j.xpro.2022.101632. PMID: PMC9405537.

Knobbe K, Partha M, Seckeler MD, Klewer S, Hsu CH, Edgin J, Morgan WJ, Provencio-Dean N, Lopez S, Parthasarathy S, Combs D. Association Between Sleep Disturbances With Neurodevelopmental Problems and Decreased Health-Related Quality of Life in Children With Fontan Circulation. *J Am Heart Assoc.* 2021 Nov 2;10(21):e021749. doi: 10.1161/JAHA.121.021749. Epub 2021 Oct 20. PMID: PMC8751823.

Koebele SV, Poisson ML, Palmer JM, Berns-Leone C, Northup-Smith SN, Peña VL, Strouse IM, Bulen HL, Patel S, Croft C, Bimonte-Nelson HA. Evaluating the Cognitive Impacts of Drospirenone, a Spironolactone-Derived Progestin, Independently and in Combination With Ethinyl Estradiol in Ovariectomized Adult Rats. *Front Neurosci.* 2022 May 25;16:885321. doi: 10.3389/fnins.2022.885321. PMID: PMC9177129.

Koebele SV, Ycaza Herrera A, Taylor CM, Barth C, Schwarz JM. Editorial: Sex Hormone Fluctuations Across the Female Lifespan: Mechanisms of Action on Brain Structure, Function, and Behavior. *Front Behav Neurosci.* 2022 Jul 5;16:964740. doi: 10.3389/fnbeh.2022.964740. PMID: PMC9296989.

Koelsch S, Andrews-Hanna JR, Skouras S. Tormenting thoughts: The posterior cingulate sulcus of the default mode network regulates valence of thoughts and activity in the brain's pain network during music listening. *Hum Brain Mapp.* 2022 Feb 1;43(2):773-786. doi: 10.1002/hbm.25686. Epub 2021 Oct 15. PMID: PMC8720190.

Kotas ME, Moore CM, Gurrola JG 2nd, Pletcher SD, Goldberg AN, Alvarez R, Yamato S, Bratcher PE, Shaughnessy CA, Zeitlin PL, Zhang IH, Li Y, Montgomery MT, Lee K, Cope EK, Locksley RM, Seibold MA, Gordon ED. IL-13-programmed airway tuft cells produce PGE₂, which promotes CFTR-dependent mucociliary function. *JCI Insight.* 2022 Jul 8;7(13):e159832. doi: 10.1172/jci.insight.159832. PMID: PMC9310525.

Kraft JN, Albizu A, O'Shea A, Hausman HK, Evangelista ND, Boutzoukas E, Hardcastle C, Van Etten EJ, Bharadwaj PK, Song H, Smith SG, DeKosky S, Hishaw GA, Wu S, Marsiske M, Cohen R, Alexander GE, Porges E, Woods AJ. Functional Neural Correlates of a Useful Field of View (UFOV)-Based fMRI Task in Older Adults. *Cereb Cortex.* 2022 Apr 20;32(9):1993-2012. doi: 10.1093/cercor/bhab332; PMID: PMC9070333.

Krell-Roesch J, Rakusa M, Syrjanen JA, van Harten AC, Lowe VJ, Jack CR Jr, Kremers WK, Knopman DS, Stokin GB, Petersen RC, Vassilaki M, Geda YE. Association between CSF biomarkers of Alzheimer's disease and neuropsychiatric symptoms: Mayo Clinic Study of Aging. *Alzheimers Dement.* 2022 Feb 9. doi: 10.1002/alz.12557. Epub ahead of print. PMID: 35142047.

Krell-Roesch J, Syrjanen JA, Bezold J, Trautwein S, Barisch-Fritz B, Boes K, Woll A, Forzani E, Kremers WK, Machulda MM, Mielke MM, Knopman DS, Petersen RC, Vassilaki M, Geda YE. Physical Activity and Trajectory of Cognitive Change in Older Persons: Mayo Clinic Study of Aging. *J Alzheimers Dis.* 2021;79(1):377-388. doi: 10.3233/JAD-200959. PMID: PMC7839815.

Kuo PH, Zukotynski K. Beyond the AJR: Tau PET, Amyloid PET, and MRI as Prognostic Markers in Early Alzheimer Disease. *AJR Am J Roentgenol.* 2022 Mar 2;1. doi: 10.2214/AJR.21.26836. Epub ahead of print. PMID: 35234499.

Langbaum JB, Zissimopoulos J, Au R, Bose N, Edgar CJ, Ehrenberg E, Fillit H, Hill CV, Hughes L, Irizarry M, Kremen S, Lakdawalla D, Lynn N, Malzbender K, Maruyama T, Massett HA, Patel D, Peneva D, Reiman EM, Romero K, Routledge C, Weiner MW, Weninger S, Aisen PS. Recommendations to address key recruitment challenges of Alzheimer's disease clinical trials. *Alzheimers Dement*. 2022 Aug 10. doi: 10.1002/alz.12737. Epub ahead of print. PMID: 35946590.

Lao Y, Cao M, Yang Y, Kishan AU, Yang W, Wang Y, Sheng K. Bladder surface dose modeling in prostate cancer radiotherapy: An analysis of motion-induced variations and the cumulative dose across the treatment. *Med Phys*. 2021 Dec;48(12):8024-8036. doi: 10.1002/mp.15326. Epub 2021 Nov 16. PMID: 35946590.

LaPlaca MC, JR Huie, HB Alam, AD Bachstetter, H Bayir, PSF Bellgowan, D Cummings, CE Dixon, AR Ferguson, C Ferland-Beckham, C Floyd, S Friess, A Galanopoulou, ED Hall, NG Harris, BE Hawkins, R Hicks, LE Hulbert, VE Johnson, P Kabitzke, AD Lafrenaye, V Lemmon, C Lifshitz, J Lifshitz, DJ Loane, L Misquitta, VC Nikolian, L Noble, DH Smith, C Taylor-Burds, N Umoh, O Vovk, AM Williams, M Young, L Zai. (2021) Pre-clinical Common Data Elements for Traumatic Brain Injury Research: Progress and Use Cases. *J. Neurotrauma* 38(10):1399-1410 PMID: 33297844. <https://doi.org/10.1089/neu.2020.7328>

Lea R, Benge JF, Adler CH, Beach TG, Belden CM, Zhang N, Shill HA, Driver-Dunckley E, Mehta SH, Atri A. An initial exploration of the convergent and ecological validity of the UDS 3.0 neuropsychological battery in Parkinson's Disease. *J Clin Exp Neuropsychol*. 2021 Nov;43(9):918-925. doi: 10.1080/13803395.2022.2034753. Epub 2022 Feb 9. PMID: 35138228

Lee H, Blumberger D, Lenze E, Anderson S, Barch D, Black K, Cristancho P, Daskalakis Z, Eisentstein S, Huang Y, Li S, Lissemore J, McConath J, Mulsant B, Raijji T, Reynolds III C, Su Y, Tu Z, Voineskos D, Karp J. Low-Dose Augmentation With Buprenorphine for Treatment-Resistant Depression: A Multisite Randomized Controlled Trial With Multimodal Assessment of Target Engagement. September 30, 2021. DOI: <https://doi.org/10.1016/j.bpsgos.2021.09.003>

Lee S, Shin Y, Cho J, Park D, & Kim C. (2022) Trabecular Bone Microarchitecture Improvement Is Associated with Skeletal Nerve Increase Following Aerobic Exercise Training in Middle-Aged Mice. *Frontiers in Physiology* Feb 22;12:800301. DOI: 10.3389/fphys.2021.800301. eCollection 2021. PMID: 35273515

Lennon KM, Saftics A, Abuelreich S, Sahu P, Lehmann HI, Maddox AL, Bagabas R, Januzzi JL, Van Keuren-Jensen K, Shah R, Das S, Jovanovic-Talisman T. Cardiac troponin T in extracellular vesicles as a novel biomarker in human cardiovascular disease. *Clin Transl Med*. 2022 Aug;12(8):e979. doi: 10.1002/ctm2.979. PMID: 35946590.

Lester E, Ooi FK, Bakkar N, Ayers J, Woerman AL, Wheeler J, Bowser R, Carlson GA, Prusiner SB, Parker R. Tau aggregates are RNA-protein assemblies that mislocalize multiple nuclear speckle components. *Neuron*. 2021 May 19;109(10):1675-1691.e9. PMID: 33848474

Levin J, Vöglein J, Quiroz YT, Bateman RJ, Ghisays V, Lopera F, McDade E, Reiman E, Tariot PN, Morris JC. Testing the amyloid cascade hypothesis: Prevention trials in autosomal dominant Alzheimer disease. *Alzheimers Dement*. 2022 Feb 24;10.1002/alz.12624. doi: 10.1002/alz.12624. Epub ahead of print. PMID: 35946590.

Lewandowski CT, Laham MS, Thatcher GRJ. Remembering your A, B, C's: Alzheimer's disease and ABCA1. *Acta Pharm Sin B*. 2022 Mar;12(3):995-1018. doi: 10.1016/j.apsb.2022.01.011. Epub 2022 Jan 24. PMID: PMC9072248.

Lewis CM, Flory JD, Moore TA, Moore AL, Rittmann BE, Vermaas WFJ, Torres CI, Fromme P. Electrochemically Driven Photosynthetic Electron Transport in Cyanobacteria Lacking Photosystem II. *J Am Chem Soc*. 2022 Feb 23;144(7):2933-2942. doi: 10.1021/jacs.1c09291. Epub 2022 Feb 14. PMID: 35157427.

Lewis CR, Bonham KS, McCann SH, Volpe AR, D'Sa V, Naymik M, De Both MD, Huentelman MJ, Lemery-Chalfant K, Highlander SK, Deoni SCL, Klepac-Ceraj V. Family SES Is Associated with the Gut Microbiome in Infants and Children. *Microorganisms*. 2021 Jul 28;9(8):1608. doi: 10.3390/microorganisms9081608. PMID: PMC8398307.

Li C, Lohrey T, Nguyen PD, Min Z, Tang Y, Ge C, Sercel ZP, McLeod E, Stoltz BM, Su J. Part-per-Trillion Trace Selective Gas Detection Using Frequency Locked Whispering-Gallery Mode Microtoroids. *ACS Appl Mater Interfaces*. 2022 Sep 1. doi: 10.1021/acsami.2c11494. Epub ahead of print. PMID: 36049126.

Li D, Zhang L, Nelson NW, Mielke MM, Yu F. Plasma Neurofilament Light and Future Declines in Cognition and Function in Alzheimer's Disease in the FIT-AD Trial. *J Alzheimers Dis Rep*. 2021 Jul 21;5(1):601-611. doi: 10.3233/ADR-210302. PMID: PMC8385429.

Li G, Manning AC, Bagi A, Yang X, Gokulnath P, Spanos M, Howard J, Chan PP, Sweeney T, Kitchen R, Li H, Laurent BD, Aranki SF, Kontaridis MI, Laurent LC, Van Keuren-Jensen K, Muehlschlegel J, Lowe TM, Das S. Distinct Stress-Dependent Signatures of Cellular and Extracellular tRNA-Derived Small RNAs. *Adv Sci (Weinh)*. 2022 Jun;9(17):e2200829. doi: 10.1002/advs.202200829. Epub 2022 Apr 4. PMID: PMC9189662.

Li R, Ding X, Geetha T, Fadamiro M, St Aubin CR, Shim M, Al-Nakkash L, Broderick TL, and Babu JR. (2022) Effects of Genistein and Exercise Training on Brain Damage Induced by a High-Fat High-Sucrose Diet in Female C57BL/ 6 Mice. *Oxidative Medicine and Cellular Longevity* 2022:1560435. PMID: 35620577

Li R, Robinson M, Ding X, Geetha T, Al-Nakkash L, Broderick TL, Babu JR. Genistein: A focus on several neurodegenerative diseases. *J Food Biochem*. 2022 Jul;46(7):e14155. doi: 10.1111/jfbc.14155. Epub 2022 Apr 22. PMID: 35460092.

Li S, An N, Chen N, Wang Y, Yang L, Wang Y, Yao Z, Hu B. The impact of Alzheimer's disease susceptibility loci on lateral ventricular surface morphology in older adults. *Brain Struct Funct*. 2022 Apr;227(3):913-924. doi: 10.1007/s00429-021-02429-y. Epub 2022 Jan 14. PMID: 35028746.

Lifshitz, J, JA Beitchman. (03/29/2022) Overt Indicators of TBI Injury in Rats. LinkedIn Post. <https://www.linkedin.com/pulse/overt-indicators-tbi-jonathan-lifshitz/>

Lifshitz, J, JA Beitchman. (04/11/2022) The Four Athletes of Concussion. LinkedIn Post. <https://www.linkedin.com/pulse/four-athletes-concussion-jonathan-lifshitz>

Liou H, Stonnington CM, Shah AA, Buckner-Petty SA, Locke DEC. Compensatory and Lifestyle-Based Brain Health Program for Subjective Cognitive Decline: Self-Implementation versus Coaching. *Brain Sci.* 2021 Sep 30;11(10):1306. doi: 10.3390/brainsci11101306. PMID: PMC8534077.

Little M, Dutta M, Li H, Matson A, Shi X, Mascarinas G, Molla B, Weigel K, Gu H, Mani S, Cui JY. Understanding the physiological functions of the host xenobiotic-sensing nuclear receptors PXR and CAR on the gut microbiome using genetically modified mice. *Acta Pharm Sin B.* 2022 Feb;12(2):801-820. doi: 10.1016/j.apsb.2021.07.022. Epub 2021 Jul 29. PMID: PMC8897037.

Liu L, Chu M, Nie B, Liu L, Xie K, Cui Y, Kong Y, Chen Z, Nan H, Chen K, Rosa-Neto P, Wu L. Reconfigured metabolism brain network in asymptomatic microtubule-associated protein tau mutation carriers: a graph theoretical analysis. *Alzheimers Res Ther.* 2022 Apr 11;14(1):52. doi: 10.1186/s13195-022-01000-z. PMID: 35410286

Liu Y, Lim K, Sundman MH, Ugonna C, Ton That V, Cowen S, Chou YH. Association Between Responsiveness to Transcranial Magnetic Stimulation and Interhemispheric Functional Connectivity of Sensorimotor Cortex in Older Adults. *Brain Connect.* 2022 Jun 27. doi: 10.1089/brain.2021.0180. Epub ahead of print. PMID: 35620910.

Locke DEC, Khayoun R, Shandera-Ochsner AL, Cuc A, Eilertsen J, Caselli M, Abrew K, Chandler MJ. Innovation Inspired by COVID: A Virtual Treatment Program for Patients With Mild Cognitive Impairment at Mayo Clinic. *Mayo Clin Proc Innov Qual Outcomes.* 2021 Oct;5(5):820-826. doi: 10.1016/j.mayocpiqo.2021.06.004. Epub 2021 Aug 17. PMID: PMC8372500.

Lorenzini L, Alsop E, Levy J, Gittings LM, Rabichow BE, Lall D, Moore S, Pevey R, Bustos L, Burciu C, Bhatia D, Singer M, Saul J, McQuade A, Tzioras M, Mota TA, Logemann A, Rose J, Almeida S, Gao FB, Marks M, Hung M, Ichida J, Bowser R, Spires-Jones T, Blurton-Jones M, Gendron TF, Baloh RH, Van Keuren-Jensen K, Sattler R. Cellular and Molecular phenotypes of C9orf72 ALS/FTD patient derived iPSC-microglia mono-cultures. *bioRxiv [Preprint]* 2020.09.03.277459; doi: <https://doi.org/10.1101/2020.09.03.277459>

Lori A, Schultebrucks K, Galatzer-Levy I, Daskalakis NP, Katrinli S, Smith AK, Myers AJ, Richholt R, Huentelman M, Guffanti G, Wuchty S, Gould F, Harvey PD, Nemeroff CB, Jovanovic T, Gerasimov ES, Maples-Keller JL, Stevens JS, Michopoulos V, Rothbaum BO, Wingo AP, Ressler KJ. Transcriptome-wide association study of post-trauma symptom trajectories identified GRIN3B as a potential biomarker for PTSD development. *Neuropsychopharmacology.* 2021 Sep;46(10):1811-1820. doi: 10.1038/s41386-021-01073-8. Epub 2021 Jun 29. PMID: PMC8357796.

Lockett PH, Chen C, Gordon BA, Wisch J, Berman SB, Chhatwal JP, Cruchaga C, Fagan AM, Farlow MR, Fox NC, Jucker M, Levin J, Masters CL, Mori H, Noble JM, Salloway S, Schofield PR, Brickman AM, Brooks WS, Cash DM, Fulham MJ, Ghetti B, Jack CR Jr, Vöglein J, Klunk WE, Koeppe R, Su Y, Weiner M, Wang Q, Marcus D, Koudelis D, Joseph-Mathurin N, Cash L, Hornbeck R, Xiong C, Perrin RJ, Karch CM, Hassenstab J, McDade E, Morris JC, Benzinger TLS, Bateman RJ,ANCES BM; Dominantly Inherited Alzheimer Network (DIAN). Biomarker clustering in autosomal dominant Alzheimer's disease. *Alzheimers Dement.* 2022 Apr 1. doi: 10.1002/alz.12661. Online ahead of print. PMID: 35362200

Luu G, Ge C, Tang Y, Li K, Cologna S, Burdette J, Su Judith*, Sanchez L.*, An integrated approach to protein discovery and detection from complex biofluids, (2022), (submitted). *co-corresponding author. *bioRxiv [Preprint]* doi: <https://doi.org/10.1101/2022.01.03.474834>

Maher EE, Kipp ZA, Leyrer-Jackson JM, Khatri S, Bondy E, Martinez GJ, Beckmann JS, Hinds TD Jr, Bimonte-Nelson HA, Gipson CD. Ovarian Hormones Regulate Nicotine Consumption and Accumbens Glutamatergic Plasticity in Female Rats. *eNeuro*. 2022 Jun 27;9(3):ENEURO.0286-21.2022. doi: 10.1523/ENEURO.0286-21.2022. PMID: PMC9239849.

Maher EE, Overby PF, Bull AH, Beckmann JS, Leyrer-Jackson JM, Koebele SV, Bimonte-Nelson HA, Gipson CD. Natural and synthetic estrogens specifically alter nicotine demand and cue-induced nicotine seeking in female rats. *Neuropharmacology*, 198:108756. doi: 10.1016/j.neuropharm.2021.108756. Epub 2021 Aug 17. PMID: PMC8484059.

Makarious MB, Leonard HL, Vitale D, Iwaki H, Sargent L, Dadu A, Violich I, Hutchins E, Saffo D, Bandres-Ciga S, Kim JJ, Song Y, Maleknia M, Bookman M, Nojopranoto W, Campbell RH, Hashemi SH, Botia JA, Carter JF, Craig DW, Van Keuren-Jensen K, Morris HR, Hardy JA, Blauwendraat C, Singleton AB, Faghri F, Nalls MA. Multi-modality machine learning predicting Parkinson's disease. *NPJ Parkinsons Dis*. 2022 Apr 1;8(1):35. doi: 10.1038/s41531-022-00288-w. PMID: PMC8975993.

Malek-Ahmadi M, Su Y, Jansen WJ. Editorial: Vascular Factors and Vascular Lesions in Pre-clinical Alzheimer's Disease. *Front Neurol*. 2021 Sep 1;12:738465. doi: 10.3389/fneur.2021.738465. eCollection 2021. PMID: 34539565

Malukiewicz J, Cartwright RA, Dergam JA, Igayara CS, Nicola PA, Pereira LMC, Ruiz-Miranda CR, Stone AC, Silva DL, Silva FFRD, Varsani A, Walter L, Wilson MA, Zinner D, Roos C. Genomic skimming and nanopore sequencing uncover cryptic hybridization in one of world's most threatened primates. *Sci Rep*. 2021 Aug 26;11(1):17279. doi: 10.1038/s41598-021-96404-6. PMID: PMC8390465.

Marballi KK, Alganem K, Brunwasser SJ, Barkatullah A, Meyers KT, Campbell JM, Ozols AB, Mccullumsmith RE, Gallitano AL. Identification of activity-induced Egr3-dependent genes reveals genes associated with DNA damage response and schizophrenia. *Transl Psychiatry*. 2022 Aug 8;12(1):320. doi: 10.1038/s41398-022-02069-8. PMID: PMC9360026.

Marinescu RV, Oxtoby NP, Young AL, Bron EE, Toga AW, Weiner MW, Barkhof F, Fox NC, and Eshaghi A, Toni T, Salaterski M, Lunina V, Ansart M, Durrleman S, Lu P, Iddi S, Li D, Thompson WK, Donohue MC, Nahon A, Levy Y, Halbersberg D, Cohen M, Liao H, Li T, Yu K, Zhu H, Tamez-Peña JG, Ismail A, Wood T, Bravo HC, Nguyen M, Sun N, Feng J, Yeo B.T. T, Chen G, Qi K, Chen S, Qiu D, Buciuman I, Kelner A, Pop R, Rimocea D, Ghazi MM, Nielsen M, Ourselin S, Sørensen L, Venkatraghavan V, Liu K, Rabe C, Manser P, Hill SM, Howlett J, Huang Z, Kiddle S, Mukherjee S, Rouanet A, Taschler B, Tom BDM, White SR, Faux N, Sedai S, de Velasco Oriol J, Clemente EEV, Estrada K, Aksman L, Altmann A, Stonnington CM, Wang Y, Wu J, Devadas V, Fourrier C, Raket LL, Sotiras A, Erus G, Doshi J, Davatzikos C, Vogel J, Doyle A, Tam A, Diaz-Papkovich A, Jammeh E, Koval I, Moore P, Lyons TJ, Gallacher J, Tohka J, Cizek R, Jedynek B, Pandya K, Bilgel M, Engels W, Cole J, Golland P, Klein S, Alexander DC, The EuroPOND Consortium, The Alzheimer's Disease Neuroimaging Initiative, The Alzheimer's Disease Prediction Of Longitudinal Evolution (TADPOLE) Challenge: Results after 1 Year Follow-up, Machine Learning for Biomedical Imaging, 1, 2021, <https://www.melba-journal.org/papers/2021:019.html>

Martinez BI, Mousa GA, Fleck K, MacCulloch T, Diehnelt CW, Stephanopoulos N, Stabenfeldt SE. Uncovering temporospatial sensitive TBI targeting strategies via in vivo phage display. *Sci Adv*. 2022 Jul 22;8(29):eabo5047. doi: 10.1126/sciadv.abo5047. Epub 2022 Jul 22. PMID: PMC9307250.

Martinez BI, Stabenfeldt SE. In Vivo Phage Display as a Biomarker Discovery Tool for the Complex Neural Injury Microenvironment. *Curr Protoc*. 2021 Feb;1(2):e67. doi: 10.1002/cpz1.67. Erratum in: *Curr Protoc*. 2022 Aug;2(8):e552. Erratum in: *Curr Protoc*. 2022 Aug;2(8):e551. PMID: 33625787.

Martin-Garcia JM, Botha S, Hu H, Jernigan R, Castellví A, Lisova S, Gil F, Calisto B, Crespo I, Roy-Chowdhury S, Grieco A, Ketawala G, Weierstall U, Spence J, Fromme P, Zatsepin N, Boer DR, Carpena X. Serial macromolecular crystallography at ALBA Synchrotron Light Source. Erratum. *J Synchrotron Radiat*. 2022 Jul 1;29(Pt 4):1130. doi: 10.1107/S1600577522005185. Epub 2022 May 16. Erratum for: *J Synchrotron Radiat*. 2022 May 1;29(Pt 3):896-907. PMID: PMC9255580.

Martin-Garcia JM, Botha S, Hu H, Jernigan R, Castellví A, Lisova S, Gil F, Calisto B, Crespo I, Roy-Chowdhury S, Grieco A, Ketawala G, Weierstall U, Spence J, Fromme P, Zatsepin N, Boer DR, Carpena X. Serial macromolecular crystallography at ALBA Synchrotron Light Source. *J Synchrotron Radiat*. 2022 May 1;29(Pt 3):896-907. doi: 10.1107/S1600577522002508. Epub 2022 Apr 4. Erratum in: *J Synchrotron Radiat*. 2022 Jul 1;29(Pt 4):1130. PMID: PMC9070724.

Martino D, Malaty I, Müller-Vahl K, Nosratmirshekarlou E, Pringsheim TM, Shprecher D, Ganos C; Movement Disorders Society Tourette Syndrome Study Group. Treatment failure in persistent tic disorders: an expert clinicians' consensus-based definition. *Eur Child Adolesc Psychiatry*. 2021 Nov 24. doi: 10.1007/s00787-021-01920-5. Online ahead of print. PMID: 34817664

Mashaqi S, Kallamadi R, Matta A, Quan SF, Patel SI, Combs D, Estep L, Lee-Iannotti J, Smith C, Parthasarathy S, Gozal D. Obstructive Sleep Apnea as a Risk Factor for COVID-19 Severity-The Gut Microbiome as a Common Player Mediating Systemic Inflammation via Gut Barrier Dysfunction. *Cells*. 2022 May 6;11(9):1569. doi: 10.3390/cells11091569. PMID: PMC9101605.

Mashaqi S, Lee-Iannotti J, Rangan P, Celaya MP, Gozal D, Quan SF, Parthasarathy S. Obstructive sleep apnea and COVID-19 clinical outcomes during hospitalization: a cohort study. *J Clin Sleep Med*. 2021 Nov 1;17(11):2197-2204. doi: 10.5664/jcsm.9424. PMID: PMC8636359.

Mateescu B, Jones JC, Alexander RP, Alsop E, An JY, Asghari M, Boomgarden A, Bouchareychas L, Cayota A, Chang HC, Charest A, Chiu DT, Coffey RJ, Das S, De Hoff P, deMello A, D'Souza-Schorey C, Elashoff D, Eliato KR, Franklin JL, Galas DJ, Gerstein MB, Ghiran IH, Go DB, Gould S, Grogan TR, Higginbotham JN, Hladik F, Huang TJ, Huo X, Hutchins E, Jeppesen DK, Jovanovic-Taliman T, Kim BYS, Kim S, Kim KM, Kim Y, Kitchen RR, Knouse V, LaPlante EL, Lebrilla CB, Lee LJ, Lennon KM, Li G, Li F, Li T, Liu T, Liu Z, Maddox AL, McCarthy K, Meechoovet B, Maniya N, Meng Y, Milosavljevic A, Min BH, Morey A, Ng M, Nolan J, De Oliveira Junior GP, Paulaitis ME, Phu TA, Raffai RL, Reátegui E, Roth ME, Routenberg DA, Rozowsky J, Rufo J, Senapati S, Shachar S, Sharma H, Sood AK, Stavakis S, Stürchler A, Tewari M, Tosar JP, Tucker-Schwartz AK, Turchinovich A, Valkov N, Van Keuren-Jensen K, Vickers KC, Vojtech L, Vreeland WN, Wang C, Wang K, Wang Z, Welsh JA, Witwer KW, Wong DTW, Xia J, Xie YH, Yang K, Zaborowski MP, Zhang C, Zhang Q, Zivkovic AM, Laurent LC. Phase 2 of extracellular RNA communication consortium charts next-generation approaches for extracellular RNA research. *iScience*. 2022 Jun 23;25(8):104653. doi: 10.1016/j.isci.2022.104653. PMID: PMC9358052.

Matijevic S, Andrews-Hanna JR, Wank AA, Ryan L, Grilli MD. Individual differences in the relationship between episodic detail generation and resting state functional connectivity vary with age. *Neuropsychologia*. 2022 Feb 10;166:108138. doi: 10.1016/j.neuropsychologia.2021.108138. Epub 2021 Dec 27. PMID: PMC8816892.

McAvan AS, Wank AA, Rapcsak SZ, Grilli MD, Ekstrom AD. Largely intact memory for spatial locations during navigation in an individual with dense amnesia. *Neuropsychologia*. 2022 Jun 6;170:108225. doi: 10.1016/j.neuropsychologia.2022.108225. Epub 2022 Mar 31. PMID: PMC9058227.

McDade E, Voytyuk I, Aisen P, Bateman RJ, Carrillo MC, De Strooper B, Haass C, Reiman EM, Sperling R, Tariot PN, Yan R, Masters CL, Vassar R, Lichtenthaler SF. The case for low-level BACE1 inhibition for the prevention of Alzheimer disease. *Nat Rev Neurol*. 2021 Nov;17(11):703-714. doi: 10.1038/s41582-021-00545-1. Epub 2021 Sep 21. PMID: 34548654.

Mendsaikhan A, Tooyama I, Serrano GE, Beach TG, Walker DG. Loss of Lysosomal Proteins Progranulin and Prosaposin Associated with Increased Neurofibrillary Tangle Development in Alzheimer Disease. *J Neuropathol Exp Neurol*. 2021 Sep 10;80(8):741-753. doi: 10.1093/jnen/nlab056. PMID: 34374777

Milicic L, Vacher M, Porter T, Doré V, Burnham SC, Bourgeat P, Shishegar R, Doecke J, Armstrong NJ, Tankard R, Maruff P, Masters CL, Rowe CC, Villemagne VL, Laws SM; Alzheimer's Disease Neuroimaging Initiative (ADNI); Australian Imaging Biomarkers and Lifestyle (AIBL) Study. Comprehensive analysis of epigenetic clocks reveals associations between disproportionate biological ageing and hippocampal volume. *Geroscience*. 2022 Jun;44(3):1807-1823. doi: 10.1007/s11357-022-00558-8. Epub 2022 Apr 21. PMID: 35445885

Miller E, Barragan V, Chiriboga J, Weddell C, Luna L, Jiménez DJ, Aleman J, Mihaljevic JR, Olivas S, Marks J, Izurieta R, Nieto N, Keim P, Trueba G, Caporaso JG, Pearson T. *Leptospira* in river and soil in a highly endemic area of Ecuador. *BMC Microbiol*. 2021 Jan 7;21(1):17. doi: 10.1186/s12866-020-02069-y. PMID: PMC7792295.

Miller SJ, Wray S, Sattler R, Zhang C. Editorial: Mechanisms of Action in Neurodegenerative Proteinopathies. *Front Neurosci*. 2022 Jun 30;16:968994. doi: 10.3389/fnins.2022.968994. PMID: PMC9281547.

Mishra A, Wang Y, Yin F, Vitali F, Rodgers KE, Soto M, Mosconi L, Wang T, Brinton RD. A tale of two systems: Lessons learned from female mid-life aging with implications for Alzheimer's prevention & treatment. *Ageing Res Rev*. 2022 Feb;74:101542. doi: 10.1016/j.arr.2021.101542. Epub 2021 Dec 17. PMID: PMC8884386.

Moghadas, B, Bharadwaj, VN, Tobey, JP, Tian, Y, Stabenfeldt, SE, Kodibagkar, VD*. GdDO3NI allows imaging of hypoxia after brain injury. *Journal of Magnetic Resonance Imaging*. 2022. 55(4): 1161-1168. DOI: 10.1002/jmri.27912. PMID: 34499791

Mollasalehi N, Francois-Moutal L, Porciani D, Burke DH, Khanna M. Aptamers Targeting Hallmark Proteins of Neurodegeneration. *Nucleic Acid Ther*. 2022 Aug;32(4):235-250. doi: 10.1089/nat.2021.0091. Epub 2022 Apr 22. PMID: 35452303.

Moreno DG, Utagawa EC, Arva NC, Schafernak KT, Mufson EJ, Perez SE. Postnatal Cytoarchitecture and Neurochemical Hippocampal Dysfunction in Down Syndrome. *J Clin Med*. 2021 Jul 31;10(15):3414. doi: 10.3390/jcm10153414. PMID: PMC8347520.

Morshed N, Lee MJ, Rodriguez FH, Lauffenburger DA, Mastroeni D, White FM. Quantitative phosphoproteomics uncovers dysregulated kinase networks in Alzheimer's disease. *Nat Aging* 1, 550–565 (2021). <https://doi.org/10.1038/s43587-021-00071-1>

Mortby ME, Adler L, Agüera-Ortiz L, Bateman DR, Brodaty H, Cantillon M, Geda YE, Ismail Z, Lanctôt KL, Marshall GA, Padala PR, Politis A, Rosenberg PB, Siarkos K, Sultzer DL, Theleritis C; ISTAART NPS PIA. Apathy as a Treatment Target in Alzheimer's Disease: Implications for Clinical Trials. *Am J Geriatr Psychiatry*. 2022 Feb;30(2):119-147. doi: 10.1016/j.jagp.2021.06.016. Epub 2021 Jul 1. PMID: 34315645.

Mufson EJ, Ginsberg SD, Ma T, Ledreux A, Perez SE. Editorial: Down Syndrome, Neurodegeneration and Dementia. *Front Aging Neurosci*. 2021 Dec 9;13:791044. doi: 10.3389/fnagi.2021.791044. PMID: 34315645. PMCID: PMC8715919.

Mufson EJ, Kelley C, Perez SE. Chronic traumatic encephalopathy and the nucleus basalis of Meynert. *Handb Clin Neurol*. 2021;182:9-29. doi: 10.1016/B978-0-12-819973-2.00002-2. PMID: 34266614.

Mullins VA, Graham S, Cummings D, Wood A, Ovando V, Skulas-Ray AC, Polian D, Wang Y, Hernandez GD, Lopez CM, Raikes AC, Brinton RD, Chilton FH. Effects of Fish Oil on Biomarkers of Axonal Injury and Inflammation in American Football Players: A Placebo-Controlled Randomized Controlled Trial. *Nutrients*. 2022 May 20;14(10):2139. doi: 10.3390/nu14102139. PMID: 353146417. PMCID: PMC9146417.

Nagaratnam N, Martin-Garcia JM, Yang JH, Goode MR, Ketawala G, Craciunescu FM, Zook JD, Sonowal M, Williams D, Grant TD, Fromme R, Hansen DT, Fromme P. Structural and biophysical properties of FopA, a major outer membrane protein of *Francisella tularensis*. *PLoS One*. 2022 Aug 1;17(8):e0267370. doi: 10.1371/journal.pone.0267370. PMID: 35842783. PMCID: PMC9342783.

Negri S, Samuel TJ, Lee S. The Potential Role of Exercise Training and Mechanical Loading on Bone-Associated Skeletal Nerves. *J Bone Metab*. 2021 Nov;28(4):267-277. doi: 10.11005/jbm.2021.28.4.267. Epub 2021 Nov 30. PMID: 348671028. PMCID: PMC8671028.

Neill M, Fisher JM, Brand C, Lei H, Sherman SJ, Chou YH, Kuo PH. Practical Application of DaTQUANT with Optimal Threshold for Diagnostic Accuracy of Dopamine Transporter SPECT. *Tomography*. 2021 Dec 18;7(4):980-989. doi: 10.3390/tomography7040081. PMID: 348706562. PMCID: PMC8706562.

Neudorfer C, Elias GJB, Jakobs M, Boutet A, Germann J, Narang K, Loh A, Paff M, Horn A, Kucharczyk W, Deeb W, Salvato B, Almeida L, Foote KD, Rosenberg PB, Tang-Wai DF, Anderson WS, Mari Z, Ponce FA, Wolk DA, Burke AD, Salloway S, Sabbagh MN, Chakravarty MM, Smith GS, Lyketsos CG, Okun MS, Lozano AM. Mapping autonomic, mood and cognitive effects of hypothalamic region deep brain stimulation. *Brain*. 2021 Oct 22;144(9):2837-2851. doi: 10.1093/brain/awab170. PMID: 348557336. PMCID: PMC8557336.

Nirogi R, Ieni J, Goyal VK, Ravula J, Jetta S, Shinde A, Jayarajan P, Benade V, Palacharla VRC, Dogiparti DK, Jasti V, Atri A, Cummings J. Effect of masupirdine (SUVN-502) on cognition in patients with moderate Alzheimer's disease: A randomized, double-blind, phase 2, proof-of-concept study. *Alzheimers Dement (N Y)*. 2022 Jun 1;8(1):e12307. doi: 10.1002/trc2.12307. eCollection 2022. PMID: 35662833. PMCID: PMC8719351.

Novotný JS, Gonzalez-Rivas JP, Medina-Inojosa JR, Lopez-Jimenez F, Geda YE, Stokin GB. Investigating cognition in midlife. *Alzheimers Dement (N Y)*. 2021 Dec 31;7(1):e12234. doi: 10.1002/trc2.12234. PMID: 348719351. PMCID: PMC8719351.

Novotný JS, Gonzalez-Rivas JP, Vassilaki M, Krell-Roesch J, Geda YE, Stokin GB. Natural Pattern of Cognitive Aging. *J Alzheimers Dis.* 2022;88(3):1147-1155. doi: 10.3233/JAD-220312. PMID: 35754277.

Olivier GN, Paul SS, Walter CS, Hayes HA, Foreman KB, Duff K, Schaefer SY, Dibble LE. The feasibility and efficacy of a serial reaction time task that measures motor learning of anticipatory stepping. *Gait Posture.* 2021 May;86:346-353. doi: 10.1016/j.gaitpost.2021.04.002. Epub 2021 Apr 7. PMID: PMC8092847.

Olney KC, Todd KT, Pallegar PN, Jensen TD, Cadiz MP, Gibson KA, Barnett JH, de Ávila C, Bouchal SM, Rabichow BE, Ding Z, Wojtas AM, Wilson MA, Fryer JD. Widespread choroid plexus contamination in sampling and profiling of brain tissue. *Mol Psychiatry.* 2022 Mar;27(3):1839-1847. doi: 10.1038/s41380-021-01416-3. Epub 2022 Jan 5. PMID: PMC9095494.

Olson TL, Zhang S, Labban D, Kaschner E, Aceves M, Iyer S, Meza-Aguilar JD, Zook JD, Chun E, Craciunescu FM, Liu W, Shi CX, Stewart AK, Hansen DT, Meurice N, Fromme P. Protein expression and purification of G-protein coupled receptor kinase 6 (GRK6), toward structure-based drug design and discovery for multiple myeloma. *Protein Expr Purif.* 2021 Sep;185:105890. doi: 10.1016/j.pep.2021.105890. Epub 2021 May 7. PMID: 33971243.

O'Mara Kunz EM, Goodnight JA, Wilson MA. The pregnancy compensation hypothesis, not the staying alive theory, accounts for disparate autoimmune functioning of women around the world. *Behav Brain Sci.* 2022 Jul 25;45:e145. doi: 10.1017/S0140525X22000589. PMID: 35875971.

Ottoy J, Ozzoude M, Zukotynski K, Adamo S, Scott C, Gaudet V, Ramirez J, Swardfager W, Cogo-Moreira H, Lam B, Bhan A, Mojiri P, Kang MS, Rabin JS, Kiss A, Strother S, Bocti C, Borrie M, Chertkow H, Frayne R, Hsiung R, Laforce RJ, Noseworthy MD, Prato FS, Sahlas DJ, Smith EE, Kuo PH, Sossi V, Thiel A, Soucy JP, Tardif JC, Black SE, Goubran M; Medical Imaging Trial Network of Canada (MITNEC) and Alzheimer's Disease Neuroimaging Initiative (ADNI). Vascular burden and cognition: Mediating roles of neurodegeneration and amyloid PET. *Alzheimers Dement.* 2022 Sep 1. doi: 10.1002/alz.12750. Epub ahead of print. PMID: 36047604.

Ozlen H, Pichet Binette A, Köbe T, Meyer PF, Gonneaud J, St-Onge F, Provost K, Soucy JP, Rosa-Neto P, Breitner J, Poirier J, Villeneuve S; Alzheimer's Disease Neuroimaging Initiative, the Harvard Aging Brain Study, the Presymptomatic Evaluation of Experimental or Novel Treatments for Alzheimer Disease Research Group. Spatial Extent of Amyloid- β Levels and Associations With Tau-PET and Cognition. *JAMA Neurol.* 2022 Aug 22. doi: 10.1001/jamaneurol.2022.2442. Epub ahead of print. PMID: 35994280.

Pandey S, Calvey G, Katz AM, Malla TN, Koua FHM, Martin-Garcia JM, Poudyal I, Yang JH, Vakili M, Yefanov O, Zielinski KA, Bajt S, Awel S, Doerner K, Frank M, Gelisio L, Jernigan R, Kirkwood H, Kloos M, Koliyadu J, Mariani V, Miller MD, Mills G, Nelson G, Olmos JL Jr, Sadri A, Sato T, Tolstikova A, Xu W, Ourmazd A, Spence JCH, Schwander P, Barty A, Chapman HN, Fromme P, Mancuso AP, Phillips GN Jr, Bean R, Pollack L, Schmidt M. Observation of substrate diffusion and ligand binding in enzyme crystals using high-repetition-rate mix-and-inject serial crystallography. *IUCrJ.* 2021 Sep 9;8(Pt 6):878-895. doi: 10.1107/S2052252521008125. PMID: PMC8562667.

Pandey S, Snider AD, Moreno WA, Ravi H, Bilgin A, Raghunand N. Joint total variation-based reconstruction of multiparametric magnetic resonance images for mapping tissue types. *NMR Biomed.* 2021 Dec;34(12):e4597. doi: 10.1002/nbm.4597. Epub 2021 Aug 13. PMID: 34390047.

Parker-Character J, Hager DR, Call TB, Pickup ZS, Turnbull SA, Marshman EM, Korch SB, Chaston JM, Call GB. An altered microbiome in a Parkinson's disease model *Drosophila melanogaster* has a negative effect on development. *Sci Rep*. 2021 Dec 8;11(1):23635. doi: 10.1038/s41598-021-02624-1. PMCID: PMC8654912.

Parkinson Study Group SURE-PD3 Investigators, Schwarzschild MA, Ascherio A, Casaceli C, Curhan GC, Fitzgerald R, Kamp C, Lungu C, Macklin EA, Marek K, Mozaffarian D, Oakes D, Rudolph A, Shoulson I, Videnovic A, Scott B, Gauger L, Aldred J, Bixby M, Ciccarello J, Gunzler SA, Henchcliffe C, Brodsky M, Keith K, Hauser RA, Goetz C, LeDoux MS, Hinson V, Kumar R, Espay AJ, Jimenez-Shahed J, Hunter C, Christine C, Daley A, Leehey M, de Marcaida JA, Friedman JH, Hung A, Bwala G, Litvan I, Simon DK, Simuni T, Poon C, Schiess MC, Chou K, Park A, Bhatti D, Peterson C, Criswell SR, Rosenthal L, Durphy J, Shill HA, Mehta SH, Ahmed A, Deik AF, Fang JY, Stover N, Zhang L, Dewey RB Jr, Gerald A, Boyd JT, Houston E, Suski V, Mosovsky S, Cloud L, Shah BB, Saint-Hilaire M, James R, Zauber SE, Reich S, Shprecher D, Pahwa R, Langhammer A, LaFaver K, LeWitt PA, Kaminski P, Goudreau J, Russell D, Houghton DJ, Laroche A, Thomas K, McGraw M, Mari Z, Serrano C, Blindauer K, Rabin M, Kurlan R, Morgan JC, Soileau M, Ainslie M, Bodis-Wollner I, Schneider RB, Waters C, Ratel AS, Beck CA, Bolger P, Callahan KF, Crotty GF, Klements D, Kostrzebski M, McMahon GM, Pothier L, Waikar SS, Lang A, Mestre T. Effect of Urate-Elevating Inosine on Early Parkinson Disease Progression: The SURE-PD3 Randomized Clinical Trial. *JAMA*. 2021 Sep 14;326(10):926-939. doi: 10.1001/jama.2021.10207. PMID: 34519802

Parpura V, Caceres H, Sims S, Ver Hoef L, Ramaniharan AK, Merritt S, Rezaei RF, Bharadwaj PK, Franchetti MK, Raichlen DA, Jessup CJ, Hishaw GA, Van Etten EJ, Trouard TP, Geldmacher DS, Wadley VG, Alperin N, Proges ES, Woods AJ, Cohen RA, Levin BE, Rundek T, Alexander GE, Visscher KM. (2022) Larger and more dentated hippocampal structure is associated with better memory in the oldest-old. *bioRxiv* [Preprint] 2022.04.10.487750.

Parra KL, Alexander GE, Raichlen DA, Klimentidis YC, Furlong MA. Exposure to air pollution and risk of incident dementia in the UK Biobank. *Environ Res*. 2022 Jun;209:112895. doi: 10.1016/j.envres.2022.112895. Epub 2022 Feb 8. PMCID: PMC8976829.

Patel SI, Zareba W, LaFleur B, Couderc JP, Xia X, Woosley R, Patel IY, Combs D, Mashaqi S, Quan SF, Parthasarathy S. Markers of ventricular repolarization and overall mortality in sleep disordered breathing. *Sleep Med*. 2022 Jul;95:9-15. doi: 10.1016/j.sleep.2022.04.016. Epub 2022 Apr 22. PMID: 35533628.

Patterson J, Shi X, Bresette W, Eghlimi R, Atlas S, Farr K, Vega-López S, Gu H. A Metabolomic Analysis of the Sex-Dependent Hispanic Paradox. *Metabolites*. 2021 Aug 20;11(8):552. doi: 10.3390/metabo11080552. PMCID: PMC8401672.

Peña M, Petrillo K, Bosset M, Fain M, Chou YH, Rapcsak S, Toosizadeh N. Brain function complexity during dual-tasking is associated with cognitive impairment and age. *J Neuroimaging*. 2022 Jul 17. doi: 10.1111/jon.13025. Epub ahead of print. PMID: 35843726.

Peters EC, Gee MT, Pawlowski LN, Kath AM, Polk FD, Vance CJ, Sacoman JL, Pires PW. Amyloid- β disrupts unitary calcium entry through endothelial NMDA receptors in mouse cerebral arteries. *J Cereb Blood Flow Metab*. 2022 Jan;42(1):145-161. doi: 10.1177/0271678X211039592. Epub 2021 Aug 31. PMCID: PMC8721780.

Petrov ME, Jiao N, Panchanathan SS, Reifsnider E, Coonrod DV, Liu L, Krajmalnik-Brown R, Gu H, Davidson LA, Chapkin RS, Whisner CM. Protocol of the Snuggle Bug/Acurrucadito Study: a longitudinal study investigating the influences of sleep-wake patterns and gut microbiome development in infancy on rapid weight gain, an early risk factor for obesity. *BMC Pediatr.* 2021 Aug 31;21(1):374. doi: 10.1186/s12887-021-02832-8. PMCID: PMC8405858.

Phatak VS, Smith GE, Locke D, Shandera-Ochsner A, Dean PM, Ball C, Gutierrez G, Chandler MJ. Computerized Cognitive Training (CCT) versus Yoga Impact on 12 Month Post Intervention Cognitive Outcome in Individuals with Mild Cognitive Impairment. *Brain Sci.* 2021 Jul 27;11(8):988. doi: 10.3390/brainsci11080988. PMCID: PMC8393756.

Phung TN, Olney KC, Pinto BJ, Silasi M, Perley L, O'Bryan J, Kliman HJ, Wilson MA. X chromosome inactivation in the human placenta is patchy and distinct from adult tissues. *HGG Adv.* 2022 May 23;3(3):100121. doi: 10.1016/j.xhgg.2022.100121. PMCID: PMC9194956.

Pink A, Krell-Roesch J, Syrjanen JA, Vassilaki M, Lowe VJ, Vemuri P, Stokin GB, Christianson TJ, Kremers WK, Jack CR, Knopman DS, Petersen RC, Geda YE. A longitudinal investigation of A β , anxiety, depression, and mild cognitive impairment. *Alzheimers Dement.* 2021 Dec 8. doi:10.1002/alz.12504. Epub ahead of print. PMID: 34877794

Piras IS, Huentelman MJ, Pinna F, Paribello P, Solmi M, Murru A, Carpiello B, Manchia M, Zai CC. A review and meta-analysis of gene expression profiles in suicide. *Eur Neuropsychopharmacol.* 2022 Mar;56:39-49. doi: 10.1016/j.euroneuro.2021.12.003. Epub 2021 Dec 16. PMID: 34923210.

Piras IS, Huentelman MJ, Walker JE, Arce R, Glass MJ, Vargas D, Sue LI, Intorcchia AJ, Nelson CM, Suszczewicz KE, Borja CL, Desforges M, Deture M, Dickson DW, Beach TG, Serrano GE. Olfactory Bulb and Amygdala Gene Expression Changes in Subjects Dying with COVID-19. *medRxiv.* 2021 Sep 15:2021.09.12.21263291. doi: 10.1101/2021.09.12.21263291. Preprint. PMID: 34545375

Piras IS, Manti F, Costa A, Carone V, Scalese B, Talboom JS, Veronesi C, Tabolacci C, Persico AM, Huentelman MJ, Sacco R, Lintas C. Molecular biomarkers to track clinical improvement following an integrative treatment model in autistic toddlers. *Acta Neuropsychiatr.* 2021 Oct;33(5):267-272. doi: 10.1017/neu.2021.12. Epub 2021 Apr 30. PMID: 33928890.

Piras IS, Raju A, Don J, Schork NJ, Gerhard GS, DiStefano JK. Hepatic PEMT Expression Decreases with Increasing NAFLD Severity. *Int J Mol Sci.* 2022 Aug 18;23(16):9296. doi: 10.3390/ijms23169296. PMCID: PMC9409182.

Poole J, Jasbi P, Pascual AS, North S, Kwatra N, Weissig V, Gu H, Bottiglieri T, Jadavji NM. Ischemic Stroke and Dietary Vitamin B12 Deficiency in Old-Aged Females: Impaired Motor Function, Increased Ischemic Damage Size, and Changed Metabolite Profiles in Brain and Cecum Tissue. *Nutrients.* 2022 Jul 19;14(14):2960. doi: 10.3390/nu14142960. PMCID: PMC9318046.

Postuma R, Fantini ML, Pereira B, Choudhury P, Lee-Iannotti J. Development and Description of the International RBD Study Group RBD Symptom Severity Scale (P2-7.004). *Neurology.* 2022 May 3;98(18 Supplement):3980.

Powers BE, Velazquez R, Strawderman MS, Ginsberg SD, Mufson EJ, Strupp BJ. Maternal Choline Supplementation as a Potential Therapy for Down Syndrome: Assessment of Effects Throughout the Lifespan. *Front Aging Neurosci.* 2021 Oct 6;13:723046. doi: 10.3389/fnagi.2021.723046. PMID: PMC8527982.

Pruzin JJ, Klein H, Rabin JS, Schultz AP, Kirn DR, Yang HS, Buckley RF, Scott MR, Properzi M, Rentz DM, Johnson KA, Sperling RA, Chhatwal JP. Physical activity is associated with increased resting-state functional connectivity in networks predictive of cognitive decline in clinically unimpaired older adults. *Alzheimers Dement (Amst).* 2022 Jul 7;14(1):e12319. doi: 10.1002/dad2.12319. eCollection 2022. PMID: 35821672

Psaltis AJ, Mackenzie BW, Cope EK, Ramakrishnan VR. Unraveling the role of the microbiome in chronic rhinosinusitis. *J Allergy Clin Immunol.* 2022 May;149(5):1513-1521. doi: 10.1016/j.jaci.2022.02.022. Epub 2022 Mar 14. PMID: PMC9354834.

Qi G, Mi Y, Yin F. Characterizing Brain Metabolic Function Ex Vivo with Acute Mouse Slice Punches. *STAR Protoc.* 2021 May 23;2(2):100559. PMID: PMC8144746.

Queder N, Phelan MJ, Taylor L, Tustison N, Doran E, Hom C, Nguyen D, Lai F, Pulsifer M, Price J, Kreisl WC, Rosas HD, Krinsky-McHale S, Brickman AM, Yassa MA, Schupf N, Silverman W, Lott IT, Head E, Mapstone M, Keator DB; Alzheimer's Biomarkers Consortium. Joint-label fusion brain atlases for dementia research in Down syndrome. *Alzheimers Dement (Amst).* 2022 May 25;14(1):e12324. doi: 10.1002/dad2.12324. eCollection 2022. PMID: 35634535

Rabin JS, Pruzin J, Scott M, Yang HS, Hampton O, Hsieh S, Schultz AP, Buckley RF, Hedden T, Rentz D, Johnson KA, Sperling RA, Chhatwal JP. Association of β -Amyloid and Vascular Risk on Longitudinal Patterns of Brain Atrophy. *Neurology.* 2022 Apr 26;10.1212/WNL.0000000000200551. doi: 10.1212/WNL.0000000000200551. Online ahead of print. PMID: 35473760

Raffaelli Q, Mills C, de Stefano NA, Mehl MR, Chambers K, Fitzgerald SA, Wilcox R, Christoff K, Andrews ES, Grilli MD, O'Connor MF, Andrews-Hanna JR. The think aloud paradigm reveals differences in the content, dynamics and conceptual scope of resting state thought in trait brooding. *Sci Rep.* 2021 Sep 30;11(1):19362. doi: 10.1038/s41598-021-98138-x. PMID: PMC8484343.

Rafii MS, Sol O, Mobley WC, Delpretti S, Skotko BG, Burke AD, Sabbagh MN, Yuan SH, Rissman RA, Pulsifer M, Evans C, Evans AC, Beth G, Fournier N, Gray JA, Dos Santos AM, Hliva V, Vukicevic M, Kosco-Vilbois M, Streffer J, Pfeifer A, Feldman HH. Safety, Tolerability, and Immunogenicity of the ACl-24 Vaccine in Adults With Down Syndrome: A Phase 1b Randomized Clinical Trial. *JAMA Neurol.* 2022 Jun 1;79(6):565-574. doi: 10.1001/jamaneurol.2022.0983. PMID: PMC9086937.

Ragunathan S, Bell LC, Semmineh N, Stokes AM, Shefner JM, Bowser R, Ladha S, Quarles CC. Evaluation of Amyotrophic Lateral Sclerosis-Induced Muscle Degeneration Using Magnetic Resonance-Based Relaxivity Contrast Imaging (RCI). *Tomography.* 2021 May 5;7(2):169-179. doi: 10.3390/tomography7020015. PMID: PMC8162571.

Raichlen DA, Furlong M, Klimentidis YC, Sayre MK, Parra KL, Bharadwaj PK, Wilcox RR, Alexander GE. Association of Physical Activity with Incidence of Dementia Is Attenuated by Air Pollution. *Med Sci Sports Exerc.* 2022 Jul 1;54(7):1131-1138. doi: 10.1249/MSS.0000000000002888. Epub 2022 Feb 8. PMID: PMC9204780.

Raichlen DA, Klimentidis YC, Sayre MK, Bharadwaj PK, Lai MHC, Wilcox RR, Alexander GE. Leisure-time sedentary behaviors are differentially associated with all-cause dementia regardless of engagement in physical activity. *Proc Natl Acad Sci U S A*. 2022 Aug 30;119(35):e2206931119. doi: 10.1073/pnas.2206931119. Epub 2022 Aug 22. PMID: PMC9436362.

Raikes AC, Hernandez GD, Matthews DC, Lukic AS, Law M, Shi Y, Schneider LS, Brinton RD. Exploratory imaging outcomes of a phase 1b/2a clinical trial of allopregnanolone as a regenerative therapeutic for Alzheimer's disease: Structural effects and functional connectivity outcomes. *Alzheimers Dement (N Y)*. 2022 Mar 14;8(1):e12258. doi: 10.1002/trc2.12258. Erratum in: *Alzheimers Dement (N Y)*. 2022 Jul 26;8(1):e12300. PMID: PMC8919249.

Ramsey K, Belnap N, Bonfitto A, Jepsen W, Naymik M, Sanchez-Castillo M, Craig DW, Szelinger S, Huentelman MJ, Narayanan V, Rangasamy S. Progressive cerebellar atrophy caused by heterozygous TECPR2 mutations. *Mol Genet Genomic Med*. 2022 Feb;10(2):e1857. doi: 10.1002/mgg3.1857. Epub 2022 Jan 7. PMID: PMC8830808.

Rando HM, Wellhausen N, Ghosh S, Lee AJ, Dattoli AA, Hu F, Byrd JB, Rafizadeh DN, Lordan R, Qi Y, Sun Y, Brueffer C, Field JM, Ben Guebila M, Jadavji NM, Skelly AN, Ramsundar B, Wang J, Goel RR, Park Y; COVID-19 Review Consortium Vikas Bansal, John P. Barton, Simina M. Boca, Joel D. Boerckel, Christian Brueffer, James Brian Byrd, Stephen Capone, Shikta Das, Anna Ada Dattoli, John J. Dziak, Jeffrey M. Field, Soumita Ghosh, Anthony Gitter, Rishi Raj Goel, Casey S. Greene, Marouen Ben Guebila, Daniel S. Himmelstein, Fengling Hu, Nafisa M. Jadavji, Jeremy P. Kamil, Sergey Knyazev, Likhitha Kolla, Alexandra J. Lee, Ronan Lordan, Tiago Lubiana, Temitayo Lukan, Adam L. MacLean, David Mai, Serghei Mangul, David Manheim, Lucy D'Agostino McGowan, Amruta Naik, YoSon Park, Dimitri Perrin, Yanjun Qi, Diane N. Rafizadeh, Bharath Ramsundar, Halie M. Rando, Sandipan Ray, Michael P. Robson, Vincent Rubinetti, Elizabeth Sell, Lamonica Shinholster, Ashwin N. Skelly, Yuchen Sun, Yusha Sun, Gregory L. Szeto, Ryan Velazquez, Jinhui Wang, Nils Wellhausen, Boca SM, Gitter A, Greene CS. Identification and Development of Therapeutics for COVID-19. *mSystems*. 2021 Dec 21;6(6):e0023321. doi: 10.1128/mSystems.00233-21. Epub 2021 Nov 2. PMID: PMC8562484.

Rangarajan V, Schreiber JJ, Barragan B, Schaefer SY, Honeycutt CF. Delays in the Reticulospinal System Are Associated With a Reduced Capacity to Learn a Simulated Feeding Task in Older Adults. *Front Neural Circuits*. 2022 Jan 27;15:681706. doi: 10.3389/fncir.2021.681706. PMID: PMC8829385.

Reho P, Koga S, Shah Z, Chia R; International LBD Genomics Consortium; American Genome Center, Rademakers R, Dalgard CL, Boeve BF, Beach TG, Dickson DW, Ross OA, Scholz SW. GRN Mutations Are Associated with Lewy Body Dementia. *Mov Disord*. 2022 Jul 10. doi: 10.1002/mds.29144. Epub ahead of print. PMID: 35810449.

Reiman EM, Mattke S, Kordower JH, Khachaturian ZS, Khachaturian AS. Developing a pathway to support the appropriate, affordable, and widespread use of effective Alzheimer's prevention drugs. *Alzheimers Dement*. 2022 Jan;18(1):7-9. doi: 10.1002/alz.12533. Epub 2022 Feb 1. PMID: 35103395.

Restifo LL. Unraveling the Gordian knot: genetics and the troubled road to effective therapeutics for Alzheimer's disease. *Genetics*. 2022 Jan 4;220(1):iyab185. doi: 10.1093/genetics/iyab185. PMID: PMC8733445.

Roemer SF, Grinberg LT, Crary JF, Seeley WW, McKee AC, Kovacs GG, Beach TG, Duyckaerts C, Ferrer IA, Gelpi E, Lee EB, Revesz T, White CL 3rd, Yoshida M, Pereira FL, Whitney K, Ghayal NB, Dickson DW. Rainwater Charitable Foundation criteria for the neuropathologic diagnosis of progressive supranuclear palsy. *Acta Neuropathol.* 2022 Aug 10. doi: 10.1007/s00401-022-02479-4. Epub ahead of print. PMID: 35947184.

Röltgen K, Nielsen SCA, Silva O, Younes SF, Zaslavsky M, Costales C, Yang F, Wirz OF, Solis D, Hoh RA, Wang A, Arunachalam PS, Colburg D, Zhao S, Haraguchi E, Lee AS, Shah MM, Manohar M, Chang I, Gao F, Mallajosyula V, Li C, Liu J, Shoura MJ, Sindher SB, Parsons E, Dashdorj NJ, Dashdorj ND, Monroe R, Serrano GE, Beach TG, Chinthrajah RS, Charville GW, Wilbur JL, Wohlstadter JN, Davis MM, Pulendran B, Troxell ML, Sigal GB, Natkunam Y, Pinsky BA, Nadeau KC, Boyd SD. Immune imprinting, breadth of variant recognition, and germinal center response in human SARS-CoV-2 infection and vaccination. *Cell.* 2022 Mar 17;185(6):1025-1040.e14. doi: 10.1016/j.cell.2022.01.018. Epub 2022 Jan 25. PMID: 35947184.

Rouse AA, Patel AD, Kao MH. Vocal learning and flexible rhythm pattern perception are linked: Evidence from songbirds. *Proc Natl Acad Sci U S A.* 2021 Jul 20;118(29):e2026130118. doi: 10.1073/pnas.2026130118. Epub 2021 Jul 16. Erratum in: *Proc Natl Acad Sci U S A.* 2021 Oct 19;118(42): PMCID: PMC8307534.

Rowe, RK, SM Murphy, H Handmaker, J Lifshitz. (2021) Population-Level Epidemiology of Concussion Concurrent with Domestic Violence in Arizona, USA. *J Neurotrauma* 38(16): 2301-2310 PMID: 33794670. <http://doi.org/10.1089/neu.2021.0022>

Saber, M, JB Ortiz, LM Rojas Valencia, X Ma, BR Tallent, PD Adelson, RK Rowe, S Qiu, J Lifshitz. (2021) Mice Born to Mothers with Gravida Traumatic Brain Injury have Distorted Brain Circuitry and Altered Immune Responses. *J Neurotrauma* 38(20): 2862-2880 PMID: 34155930. <https://doi.org/10.1089/neu.2021.0048>

Saber, M, SM Murphy, Y Cho, J Lifshitz, RK Rowe. (2021) Experimental Diffuse Brain Injury and a Model of Alzheimer's Disease Exhibit Disease-Specific Changes in Sleep and Incongruous Peripheral Inflammation. *Journal of Neuroscience Research* 99(4) 1136-1160 PMID: 33319441 <http://dx.doi.org/10.1002/jnr.24771>

Sarabipour S, Hainer SJ, Arslan FN, de Winde CM, Furlong E, Bielczyk N, Jadavji NM, Shah AP, Davla S. Building and sustaining mentor interactions as a mentee. *FEBS J.* 2022 Mar;289(6):1374-1384. doi: 10.1111/febs.15823. Epub 2021 Apr 5. PMID: 34155930.

Sarabipour S, Hainer SJ, Furlong E, Jadavji NM, de Winde CM, Bielczyk N, Shah AP. Writing an effective and supportive recommendation letter. *FEBS J.* 2022 Jan;289(2):298-307. doi: 10.1111/febs.15757. Epub 2021 Mar 5. PMID: 34155930.

Sawa M, Overk C, Becker A, Derse D, Albay R, Weldy K, Salehi A, Beach TG, Doran E, Head E, Yu YE, Mobley WC. Impact of increased APP gene dose in Down syndrome and the Dp16 mouse model. *Alzheimers Dement.* 2022 Jun;18(6):1203-1234. doi: 10.1002/alz.12463. Epub 2021 Nov 10. PMID: 35947184.

Schaefer SY, Duff K, Hooyman A, Hoffman JM. Improving Prediction of Amyloid Deposition in Mild Cognitive Impairment With a Timed Motor Task. *Am J Alzheimers Dis Other Dement.* 2022 Jan-Dec;37:15333175211048262. doi: 10.1177/15333175211048262. PMID: 35200059.

Schaefer SY, Malek-Ahmadi M, Hooyman A, King JB, Duff K. Association Between Motor Task Performance and Hippocampal Atrophy Across Cognitively Unimpaired, Amnesic Mild Cognitive Impairment, and Alzheimer's Disease Individuals. *J Alzheimers Dis.* 2022;85(4):1411-1417. doi: 10.3233/JAD-210665. PMID: 34958015.

Schaefer SY, McCulloch KL, Lang CE. Pondering the Cognitive-Motor Interface in Neurologic Physical Therapy. *J Neurol Phys Ther.* 2022 Jan 1;46(1):1-2. doi: 10.1097/NPT.0000000000000381. PMID: 34628436.

Schafernak KT, Jacobsen JR, Hernandez D, Kaye RD, Perez SE. Cytochemical Characterization of Cerebrospinal Fluid Macrophage Inclusions in Pediatric Patients Receiving Intrathecal Nusinersen (SPINRAZA®) for Spinal Muscular Atrophy. *Acta Cytol.* 2022;66(1):79-84. doi: 10.1159/000518005. Epub 2021 Aug 17. PMID: 34515035.

Schelbaum E, Loughlin L, Jett S, Zhang C, Jang G, Malviya N, Hristov H, Pahlajani S, Isaacson R, Dyke JP, Kamel H, Brinton RD, Mosconi L. Association of Reproductive History With Brain MRI Biomarkers of Dementia Risk in Midlife. *Neurology.* 2021 Dec 7;97(23):e2328-e2339. doi: 10.1212/WNL.0000000000012941. Epub 2021 Nov 3. PMCID: PMC8665431.

Schoemaker D, Zanon Zotin MC, Chen K, Igwe KC, Vila-Castelar C, Martinez J, Baena A, Fox-Fuller JT, Lopera F, Reiman EM, Brickman AM, Quiroz YT. White matter hyperintensities are a prominent feature of autosomal dominant Alzheimer's disease that emerge prior to dementia. *Alzheimers Res Ther.* 2022 Jun 29;14(1):89. doi: 10.1186/s13195-022-01030-7. PMID: 35768838

Schwerin SC, Chatterjee M, Hutchinson EB, Djankpa FT, Armstrong RC, McCabe JT, Perl DP, Juliano SL. Expression of GFAP and Tau Following Blast Exposure in the Cerebral Cortex of Ferrets. *J Neuropathol Exp Neurol.* 2021 Jan 20;80(2):112-128. doi: 10.1093/jnen/nlaa157. PMCID: PMC8453607.

Scott GD, Arnold MR, Beach TG, Gibbons CH, Kanthasamy AG, Lebovitz RM, Lemstra AW, Shaw LM, Teunissen CE, Zetterberg H, Taylor AS, Graham TC, Boeve BF, Gomperts SN, Graff-Radford NR, Moussa C, Poston KL, Rosenthal LS, Sabbagh MN, Walsh RR, Weber MT, Armstrong MJ, Bang JA, Bozoki AC, Domoto-Reilly K, Duda JE, Fleisher JE, Galasko DR, Galvin JE, Goldman JG, Holden SK, Honig LS, Huddleston DE, Leverenz JB, Litvan I, Manning CA, Marder KS, Pantelyat AY, Pelak VS, Scharre DW, Sha SJ, Shill HA, Mari Z, Quinn JF, Irwin DJ. Fluid and Tissue Biomarkers of Lewy Body Dementia: Report of an LBDA Symposium. *Front Neurol.* 2022 Jan 31;12:805135. doi: 10.3389/fneur.2021.805135. PMCID: PMC8841880.

Sepulveda-Falla D, Sanchez JS, Almeida MC, Boassa D, Acosta-Uribe J, Vila-Castelar C, Ramirez-Gomez L, Baena A, Aguillon D, Villalba-Moreno ND, Littau JL, Villegas A, Beach TG, White CL 3rd, Ellisman M, Krasemann S, Glatzel M, Johnson KA, Sperling RA, Reiman EM, Arboleda-Velasquez JF, Kosik KS, Lopera F, Quiroz YT. Distinct tau neuropathology and cellular profiles of an APOE3 Christchurch homozygote protected against autosomal dominant Alzheimer's dementia. *Acta Neuropathol.* 2022 Sep;144(3):589-601. doi: 10.1007/s00401-022-02467-8. Epub 2022 Jul 15. PMCID: PMC9381462.

Serrano GE, Walker JE, Tremblay C, Piras IS, Huentelman MJ, Belden CM, Goldfarb D, Shprecher D, Atri A, Adler CH, Shill HA, Driver-Dunckley E, Mehta SH, Caselli R, Woodruff BK, Haarer CF, Ruhlen T, Torres M, Nguyen S, Schmitt D, Rapsack SZ, Bime C, Peters JL, Alevritis E, Arce RA, Glass MJ, Vargas D, Sue LI, Intorcchia AJ, Nelson CM, Oliver J, Russell A, Suszczewicz KE, Borja CI, Cline MP, Hemmingsen SJ, Qiji S, Hobgood HM, Mizgerd JP, Sahoo MK, Zhang H, Solis D, Montine TJ, Berry GJ, Reiman EM, Røltgen K, Boyd SD, Pinsky BA, Zehnder JL, Talbot

P, Desforges M, DeTure M, Dickson DW, Beach TG. SARS-CoV-2 Brain Regional Detection, Histopathology, Gene Expression, and Immunomodulatory Changes in Decedents with COVID-19. *J Neuropathol Exp Neurol*. 2022 Aug 16;81(9):666-695. doi: 10.1093/jnen/nlac056. PMID: PMC9278252.

Shah J, Gao F, Li B, Ghisays V, Luo J, Chen Y, Lee W, Zhou Y, Benzinger TLS, Reiman EM, Chen K, Su Y, Wu T. Deep residual inception encoder-decoder network for amyloid PET harmonization. *Alzheimers Dement*. 2022 Feb 9. doi: 10.1002/alz.12564. Online ahead of print. PMID: 35142053

Shah-Basak P, Sivaratnam G, Teti S, Deschamps T, Kielar A, Jokel R, Meltzer JA. Electrophysiological connectivity markers of preserved language functions in post-stroke aphasia. *Neuroimage Clin*. 2022;34:103036. doi: 10.1016/j.nicl.2022.103036. Epub 2022 May 7. PMID: PMC9111985.

Shandera-Ochsner AL, Chandler MJ, Locke DE, Ball CT, Crook JE, Phatak VS, Smith GE. Comparative Effects of Physical Exercise and Other Behavioral Interventions on Functional Status Outcomes in Mild Cognitive Impairment. *J Int Neuropsychol Soc*. 2021 Sep;27(8):805-812. doi: 10.1017/S1355617721000485. Epub 2021 Jul 26. PMID: PMC8458219.

Shekhar M, Terashi G, Gupta C, Sarkar D, Debussche G, Sisco NJ, Nguyen J, Mondal A, Vant J, Fromme P, Van Horn WD, Tajkhorshid E, Kihara D, Dill K, Perez A, Singharoy A. CryoFold: determining protein structures and data-guided ensembles from cryo-EM density maps. *Matter*. 2021 Oct 6;4(10):3195-3216. doi: 10.1016/j.matt.2021.09.004. Epub 2021 Sep 22. PMID: PMC9302471.

Shen XN, Huang YY, Chen SD, Guo Y, Tan L, Dong Q, Yu JT; Alzheimer's Disease Neuroimaging Initiative. Plasma phosphorylated-tau181 as a predictive biomarker for Alzheimer's amyloid, tau and FDG PET status. *Transl Psychiatry*. 2021 Nov 13;11(1):585. doi: 10.1038/s41398-021-01709-9. PMID: 34775468

Shen Z, Schutte D, Yi Y, Bompelli A, Yu F, Wang Y, Zhang R. Classifying the lifestyle status for Alzheimer's disease from clinical notes using deep learning with weak supervision. *BMC Med Inform Decis Mak*. 2022 Jul 7;22(Suppl 1):88. doi: 10.1186/s12911-022-01819-4. PMID: PMC9261217.

Shirinian M, Chen C, Uchida S, Jadavji NM. Editorial: The role of epigenetics in neuropsychiatric disorders. *Front Mol Neurosci*. 2022 Jul 25;15:985023. doi: 10.3389/fnmol.2022.985023. PMID: PMC9359137.

Signaevsky M, Marami B, Prastawa M, Tabish N, Iida MA, Zhang XF, Sawyer M, Duran I, Koenigsberg DG, Bryce CH, Chahine LM, Mollenhauer B, Mosovsky S, Riley L, Dave KD, Eberling J, Coffey CS, Adler CH, Serrano GE, White CL 3rd, Koll J, Fernandez G, Zeineh J, Cordon-Cardo C, Beach TG, Crary JF. Antemortem detection of Parkinson's disease pathology in peripheral biopsies using artificial intelligence. *Acta Neuropathol Commun*. 2022 Feb 14;10(1):21. doi: 10.1186/s40478-022-01318-7. PMID: 35164870

Sims SA, Faulkner ME, Stewart P, Merritt S, Rezaei RF, Bharadwaj PK, Franchetti MK, Raichlen DA, Jessup CJ, Hishaw GA, Van Etten EJ, Trouard TP, Geldmacher D, Wadley VG, Alperin N, Porges ES, Woods AJ, Cohen RA, Levin BE, Rundek T, Alexander GE, Visscher KM. Fronto-parietal Network Segregation Predicts Maintained Cognition in the Cognitively Healthy Oldest-old. *bioRxiv [Preprint]* 2021.10.05.463207; doi: <https://doi.org/10.1101/2021.10.05.463207>

Sims SA, Levin B, Rundek T, Cohen RA, Alexander GE, Visscher KM. A-15 Validity of the NIH Toolbox Cognitive Battery in a Healthy Oldest-Old 85+ Sample, *Archives of Clinical Neuropsychology*, Volume 36, Issue 6, September 2021, Page 1056, <https://doi.org/10.1093/arclin/acab062.33>

Sisco NJ, Wang P, Stokes AM, Dortch RD. Rapid parameter estimation for selective inversion recovery myelin imaging using an open-source Julia toolkit. *PeerJ*. 2022 Mar 29;10:e13043. doi: 10.7717/peerj.13043. PMCID: PMC8973461.

Smith GS, Workman CI, Protas H, Su Y, Savonenko A, Kuwabara H, Gould NF, Kraut M, Joo JH, Nandi A, Avramopoulos D, Reiman EM, Chen K. Positron emission tomography imaging of serotonin degeneration and beta-amyloid deposition in late-life depression evaluated with multi-modal partial least squares. *Transl Psychiatry*. 2021 Sep 13;11(1):473. doi: 10.1038/s41398-021-01539-9. PMID: 34518514

Smith RG, Pishva E, Shireby G, Smith AR, Roubroeks JAY, Hannon E, Wheildon G, Mastroeni D, Gasparoni G, Riemenschneider M, Giese A, Sharp AJ, Schalkwyk L, Haroutunian V, Viechtbauer W, van den Hove DLA, Weedon M, Brokaw D, Francis PT, Thomas AJ, Love S, Morgan K, Walter J, Coleman PD, Bennett DA, De Jager PL, Mill J, Lunnon K. A meta-analysis of epigenome-wide association studies in Alzheimer's disease highlights novel differentially methylated loci across cortex. *Nat Commun*. 2021 Jun 10;12(1):3517. doi: 10.1038/s41467-021-23243-4. PMCID: PMC8192929.

Snider JM, You JK, Wang X, Snider AJ, Hallmark B, Zec MM, Seeds MC, Sergeant S, Johnstone L, Wang Q, Sprissler R, Carr TF, Lutrick K, Parthasarathy S, Bime C, Zhang HH, Luberto C, Kew RR, Hannun YA, Guerra S, McCall CE, Yao G, Del Poeta M, Chilton FH. Group IIA secreted phospholipase A2 is associated with the pathobiology leading to COVID-19 mortality. *J Clin Invest*. 2021 Oct 1;131(19):e149236. doi: 10.1172/JCI149236. PMCID: PMC8483752.

Srinivasan G, Brafman DA. The Emergence of Model Systems to Investigate the Link Between Traumatic Brain Injury and Alzheimer's Disease. *Front Aging Neurosci*. 2022 Feb 8;13:813544. doi: 10.3389/fnagi.2021.813544. PMCID: PMC8862182.

Stokes AM, Bergamino M, Alhilali L, Hu LS, Karis JP, Baxter LC, Bell LC, Quarles CC. Evaluation of single bolus, dual-echo dynamic susceptibility contrast MRI protocols in brain tumor patients. *J Cereb Blood Flow Metab*. 2021 Dec;41(12):3378-3390. doi: 10.1177/0271678X211039597. Epub 2021 Aug 20. PMCID: PMC8669280.

Stokes AM, Rangunathan S, Robison RK, Fuentes A, Bell LC, Karis JP, Pipe JG, Quarles CC. Development of a spiral spin- and gradient-echo (spiral-SAGE) approach for improved multi-parametric dynamic contrast neuroimaging. *Magn Reson Med*. 2021 Dec;86(6):3082-3095. doi: 10.1002/mrm.28933. Epub 2021 Jul 20. PMID: 34288112.

Stonebarger GA, Bimonte-Nelson HA, Urbanski HF. The Rhesus Macaque as a Translational Model for Neurodegeneration and Alzheimer's Disease. *Front Aging Neurosci*. 2021 Sep 3;13:734173. doi: 10.3389/fnagi.2021.734173. PMCID: PMC8446616.

Storm CS, Kia DA, Almramhi MM, Bandres-Ciga S, Finan C; International Parkinson's Disease Genomics Consortium (IPDGC), Hingorani AD, Wood NW. Finding genetically-supported drug targets for Parkinson's disease using Mendelian randomization of the druggable genome. *Nat Commun*. 2021 Dec 20;12(1):7342. doi: 10.1038/s41467-021-26280-1. PMCID: PMC8688480.

Suchy-Dicey A, Howard B, Longstreth WT Jr, Reiman EM, Buchwald D. APOE genotype, hippocampus, and cognitive markers of Alzheimer's disease in American Indians: Data from the Strong Heart Study. *Alzheimers Dement.* 2022 Feb 10:10.1002/alz.12573. doi: 10.1002/alz.12573. Epub ahead of print. PMID: PMC9363523.

Suebka S, Nguyen PD, Gin A, Su J. How Fast It Can Stick: Visualizing Flow Delivery to Microtoroid Biosensors. *ACS Sens.* 2021 Jul 23;6(7):2700-2708. doi: 10.1021/acssensors.1c00748. Epub 2021 Jun 2. PMID: 34078073.

Sui J, Li X, Bell RP, Towe SL, Gadde S, Chen NK, Meade CS. Structural and Functional Brain Abnormalities in Human Immunodeficiency Virus Disease Revealed by Multimodal Magnetic Resonance Imaging Fusion: Association With Cognitive Function. *Clin Infect Dis.* 2021 Oct 5;73(7):e2287-e2293. doi: 10.1093/cid/ciaa1415. PMID: PMC8492163.

Sun Y, Zhou D, Rahman MR, Zhu J, Ghoneim D, Cox NJ, Beach TG, Wu C, Gamazon ER, Wu L. A transcriptome-wide association study identifies novel blood-based gene biomarker candidates for Alzheimer's disease risk. *Hum Mol Genet.* 2021 Dec 27;31(2):289-299. doi: 10.1093/hmg/ddab229. PMID: PMC8831284.

Sykora D, Stonnington CM, Jain N. An Agitated Patient With COVID-19 Infection and Early-onset Alzheimer Disease. *Alzheimer Dis Assoc Disord.* 2022 Jan-Mar 01;36(1):83-84. doi: 10.1097/WAD.0000000000000456. PMID: PMC8876388.

Ta AC, Huang LC, McKeown CR, Bestman JE, Van Keuren-Jensen K, Cline HT. Temporal and spatial transcriptomic dynamics across brain development in *Xenopus laevis* tadpoles. *G3 (Bethesda).* 2022 Jan 4;12(1):jkab387. doi: 10.1093/g3journal/jkab387. PMID: PMC8728038.

Ta D, Tu Y, Lu ZL, Wang Y. Quantitative characterization of the human retinotopic map based on quasiconformal mapping. *Med Image Anal.* 2022 Jan;75:102230. doi: 10.1016/j.media.2021.102230. Epub 2021 Oct 4. PMID: PMC8678293.

Tabrizi SJ, Schobel S, Gantman EC, Mansbach A, Borowsky B, Konstantinova P, Mestre TA, Panagoulas J, Ross CA, Zauderer M, Mullin AP, Romero K, Sivakumaran S, Turner EC, Long JD, Sampaio C; Huntington's Disease Regulatory Science Consortium (HD-RSC). A biological classification of Huntington's disease: the Integrated Staging System. *Lancet Neurol.* 2022 Jul;21(7):632-644. doi: 10.1016/S1474-4422(22)00120-X. PMID: 35716693.

Tahami Monfared AA, Lenderking WR, Savva Y, Ladd MK, Zhang Q; Alzheimer's Disease Neuroimaging Initiative. Assessing the Clinical Meaningfulness of the Alzheimer's Disease Composite Score (ADCOMS) Tool. *Neurol Ther.* 2022 Sep;11(3):1085-1100. doi: 10.1007/s40120-022-00352-w. Epub 2022 May 5. PMID: PMC9338189.

Tallino S, Winslow W, Bartholomew SK, Velazquez R. Temporal and brain region-specific elevations of soluble Amyloid- β 40-42 in the Ts65Dn mouse model of Down syndrome and Alzheimer's disease. *Aging Cell.* 2022 Apr;21(4):e13590. doi: 10.1111/acer.13590. Epub 2022 Mar 15. PMID: PMC9009111.

Tang H, Guo L, Fu X, Qu B, Ajilore O, Wang Y, Thompson PM, Huang H, Leow AD, Zhan L. A Hierarchical Graph Learning Model for Brain Network Regression Analysis. *Front Neurosci.* 2022 Jul 12;16:963082. doi: 10.3389/fnins.2022.963082. PMID: PMC9315240.

Targum SD, Fosdick L, Drake KE, Rosenberg PB, Burke AD, Wolk DA, Foote KD, Asaad WF, Sabbagh M, Smith GS, Lozano AM, Lyketsos CG. Effect of Age on Clinical Trial Outcome in Participants with Probable Alzheimer's Disease. *J Alzheimers Dis.* 2021;82(3):1243-1257. doi: 10.3233/JAD-210530. PMID: 34151817.

Tariot PN, Ballard C, Devanand DP, Cummings JL, Sultzer DL. Pimavanserin and dementia-related psychosis. *Lancet Neurol.* 2022 Feb;21(2):114-115. doi: 10.1016/S1474-4422(21)00466-X. PMID: 35065031.

Tello JA, Williams HE, Eppler RM, Steinhilb ML, Khanna M. Animal Models of Neurodegenerative Disease: Recent Advances in Fly Highlight Innovative Approaches to Drug Discovery. *Front Mol Neurosci.* 2022 Apr 19;15:883358. doi: 10.3389/fnmol.2022.883358. PMCID: PMC9063566.

Thomas KR, Weigand AJ, Edwards LC, Edmonds EC, Bangen KJ, Ortiz G, Walker KS, Bondi MW; Alzheimer's Disease Neuroimaging Initiative. Tau levels are higher in objective subtle cognitive decline but not subjective memory complaint. *Alzheimers Res Ther.* 2022 Aug 22;14(1):114. doi: 10.1186/s13195-022-01060-1. PMCID: PMC9394026.

Tiklová K, Gillberg L, Volakakis N, Lundén-Miguel H, Dahl L, Serrano GE, Adler CH, Beach TG, Perlmann T. Disease Duration Influences Gene Expression in Neuromelanin-Positive Cells From Parkinson's Disease Patients. *Front Mol Neurosci.* 2021 Nov 11;14:763777. doi: 10.3389/fnmol.2021.763777. eCollection 2021. PMID: 34867188

Tjandra D, Migrino RQ, Giordani B, Wiens J. Use of blood pressure measurements extracted from the electronic health record in predicting Alzheimer's disease: A retrospective cohort study at two medical centers. *Alzheimers Dement.* 2022 Apr 16. doi: 10.1002/alz.12676. Epub ahead of print. PMID: 35429343.

Todd, J, Bharadwaj, VN, Nellenbach, K, Nandi, S, Mihalko, E, Copeland, C, Brown, AC*, Stabenfeldt, SE*. Platelet-Like Particles Reduce Coagulopathy-Related and Neuroinflammatory Pathologies Post-Experimental Traumatic Brain Injury. *Journal of Biomedical Materials Research: Part B - Applied Biomaterials.* 2021;109(12): 2268-2278. DOI: 10.1002/jbm.b.34888. PMCID: PMC8490285

Torrandell-Haro G, Branigan GL, Brinton RD, Rodgers KE. Association Between Specific Type 2 Diabetes Therapies and Risk of Alzheimer's Disease and Related Dementias in Propensity-Score Matched Type 2 Diabetic Patients. *Front Aging Neurosci.* 2022 May 6;14:878304. doi: 10.3389/fnagi.2022.878304. PMCID: PMC9120543.

Tremblay C, Serrano GE, Intorcchia AJ, Curry J, Sue LI, Nelson CM, Walker JE, Glass MJ, Arce RA, Fleisher AS, Pontecorvo MJ, Atri A, Montine TJ, Chen K, Beach TG. Hemispheric Asymmetry and Atypical Lobar Progression of Alzheimer-Type Tauopathy. *J Neuropathol Exp Neurol.* 2022 Feb 24;81(3):158-171. doi: 10.1093/jnen/nlac008. PMID: 35191506

Tremblay C, Serrano GE, Intorcchia AJ, Mariner MR, Sue LI, Arce RA, Atri A, Adler CH, Belden CM, Shill HA, Driver-Dunckley E, Mehta SH, Beach TG. Olfactory Bulb Amyloid- β Correlates With Brain Thal Amyloid Phase and Severity of Cognitive Impairment. *J Neuropathol Exp Neurol.* 2022 Jun 25;nlac042. doi: 10.1093/jnen/nlac042. Online ahead of print. PMID: 35751438

Tremblay C, Serrano GE, Intorcchia AJ, Sue LI, Wilson JR, Adler CH, Shill HA, Driver-Dunckley E, Mehta SH, Beach TG. Effect of olfactory bulb pathology on olfactory function in normal aging. *Brain Pathol.* 2022 Apr 29:e13075. doi: 10.1111/bpa.13075. Online ahead of print. PMID: 35485279

Tu Y, Li X, Lu ZL, Wang Y. Diffeomorphic registration for retinotopic maps of multiple visual regions. *Brain Struct Funct.* 2022 May;227(4):1507-1522. doi: 10.1007/s00429-022-02480-3. Epub 2022 Mar 24. PMID: 35325293.

Tu Y, Li X, Lu ZL, Wang Y. Protocol for topology-preserving smoothing of BOLD fMRI retinotopic maps of the human visual cortex. *STAR Protoc.* 2022 Aug 11;3(3):101614. doi: 10.1016/j.xpro.2022.101614. PMCID: PMC9389414.

Tu Y, Ta D, Lu ZL, Wang Y. Topological Receptive Field Model for Human Retinotopic Mapping. *Med Image Comput Comput Assist Interv.* 2021;12907:639-649. doi: 10.1007/978-3-030-87234-2_60. Epub 2021 Sep 21. PMCID: PMC8570543.

Tu Y, Ta D, Lu ZL, Wang Y. Topology-preserving smoothing of retinotopic maps. *PLoS Comput Biol.* 2021 Aug 2;17(8):e1009216. doi: 10.1371/journal.pcbi.1009216. PMCID: PMC8360528.

Turner EC, Gantman EC, Sampaio C, Sivakumaran S. Huntington's Disease Regulatory Science Consortium: Accelerating Medical Product Development. *J Huntingtons Dis.* 2022;11(2):97-104. doi: 10.3233/JHD-220533. PMID: 35466945.

Umapathy L, Keerthivasan MB, Zahr NM, Bilgin A, Saranathan M. Convolutional Neural Network Based Frameworks for Fast Automatic Segmentation of Thalamic Nuclei from Native and Synthesized Contrast Structural MRI. *Neuroinformatics.* 2021 Oct 9:10.1007/s12021-021-09544-5. doi: 10.1007/s12021-021-09544-5. Epub ahead of print. PMCID: PMC8993941.

Utagawa EC, Moreno DG, Schafernak KT, Arva NC, Malek-Ahmadi MH, Mufson EJ, Perez SE. Neurogenesis and neuronal differentiation in the postnatal frontal cortex in Down syndrome. *Acta Neuropathol Commun.* 2022 Jun 8;10(1):86. doi: 10.1186/s40478-022-01385-w. PMCID: PMC9175369.

Vassilaki M, Aakre JA, Castillo A, Chamberlain AM, Wilson PM, Kremers WK, Mielke MM, Geda YE, Machulda MM, Alhurani RE, Graff-Radford J, Vemuri P, Lowe VJ, Jack CR Jr, Knopman DS, Petersen RC. Association of neighborhood socioeconomic disadvantage and cognitive impairment. *Alzheimers Dement.* 2022 Jun 6. doi: 10.1002/alz.12702. Epub ahead of print. PMID: 35666244.

Vassilaki M, Aakre JA, Kremers WK, Mielke MM, Geda YE, Machulda MM, Knopman DS, Vemuri P, Lowe VJ, Jack CR Jr, Roberson ED, Gerstenecker A, Martin RC, Kennedy RE, Marson DC, Petersen RC. Association of Performance on the Financial Capacity Instrument-Short Form With Brain Amyloid Load and Cortical Thickness in Older Adults. *Neurol Clin Pract.* 2022 Apr;12(2):113-124. doi: 10.1212/CPJ.0000000000001157. PMCID: PMC9208409.

Veldhuizen J, Chavan R, Moghadas B, Park JG, Kodibagkar VD, Migrino RQ, Nikkiah M. Cardiac ischemia on-a-chip to investigate cellular and molecular response of myocardial tissue under hypoxia. *Biomaterials.* 2022 Feb;281:121336. doi: 10.1016/j.biomaterials.2021.121336. Epub 2021 Dec 30. PMID: 35026670.

Vila-Castelar C, Tariot PN, Sink KM, Clayton D, Langbaum JB, Thomas RG, Chen Y, Su Y, Chen K, Hu N, Giraldo-Chica M, Tobón C, Acosta-Baena N, Luna E, Londoño M, Ospina P, Tirado V, Muñoz C, Henao E, Bocanegra Y, Alvarez S, Rios-Romenets S, Ghisays V, Goradia D, Lee W, Luo J, Malek-Ahmadi MH, Protas HD, Lopera F, Reiman EM, Quiroz YT; API ADAD Colombia Trial Group. Sex differences in cognitive resilience in preclinical autosomal-dominant Alzheimer's disease carriers and non-carriers: Baseline findings from the API ADAD Colombia Trial. *Alzheimers Dement*. 2022 Feb 1. doi: 10.1002/alz.12552. Online ahead of print. PMID: 35103388

Vitali F, Branigan GL, Brinton RD. Preventing Alzheimer's disease within reach by 2025: Targeted-risk-AD-prevention (TRAP) strategy. *Alzheimers Dement (N Y)*. 2021 Sep 20;7(1):e12190. doi: 10.1002/trc2.12190. PMCID: PMC8451031.

Wakeman DR, Weed MR, Perez SE, Cline EN, Viola KL, Wilcox KC, Moddrelle DS, Nisbett EZ, Kurian AM, Bell AF, Pike R, Jacobson PB, Klein WL, Mufson EJ, Lawrence MS, Elsworth JD. Intrathecal amyloid-beta oligomer administration increases tau phosphorylation in the medial temporal lobe in the African green monkey: A nonhuman primate model of Alzheimer's disease. *Neuropathol Appl Neurobiol*. 2022 Jun;48(4):e12800. doi: 10.1111/nan.12800. Epub 2022 Mar 2. PMID: 35156715.

Wang G, Zhou W, Kong D, Qu Z, Ba M, Hao J, Yao T, Dong Q, Su Y, Reiman EM, Caselli RJ, Chen K, Wang Y; Alzheimer's Disease Neuroimaging Initiative. Studying APOE ϵ 4 Allele Dose Effects with a Univariate Morphometry Biomarker. *J Alzheimers Dis*. 2022;85(3):1233-1250. doi: 10.3233/JAD-215149. PMID: 34924383.

Wang J, Cato K, Conwell Y, Yu F, Heffner K, Caprio TV, Nathan K, Monroe TB, Muench U, Li Y. Pain treatment and functional improvement in home health care: Relationship with dementia. *J Am Geriatr Soc*. 2021 Dec;69(12):3545-3556. doi: 10.1111/jgs.17420. Epub 2021 Aug 21. PMID: 34418061.

Wang J, Cheng Z, Kim Y, Yu F, Heffner KL, Quiñones-Cordero MM, Li Y. Pain and the Alzheimer's Disease and Related Dementia Spectrum in Community-Dwelling Older Americans: A Nationally Representative Study. *J Pain Symptom Manage*. 2022 May;63(5):654-664. doi: 10.1016/j.jpainsymman.2022.01.012. Epub 2022 Jan 23. PMCID: PMC9035327.

Wang J, Shen JY, Yu F, Conwell Y, Nathan K, Shah AS, Simmons SF, Li Y, Ramsdale E, Caprio TV. Medications Associated With Geriatric Syndromes (MAGS) and Hospitalization Risk in Home Health Care Patients. *J Am Med Dir Assoc*. 2022 Apr 28:S1525-8610(22)00256-0. doi: 10.1016/j.jamda.2022.03.012. Epub ahead of print. PMID: 35490716.

Wang Q, Chen G, Schindler SE, Christensen J, McKay NS, Liu J, Wang S, Sun Z, Hassenstab J, Su Y, Flores S, Hornbeck R, Cash L, Cruchaga C, Fagan AM, Tu Z, Morris JC, Mintun MA, Wang Y, Benzinger TLS. Baseline Microglial Activation Correlates With Brain Amyloidosis and Longitudinal Cognitive Decline in Alzheimer Disease. *Neurol Neuroimmunol Neuroinflamm*. 2022 Mar 8;9(3):e1152. doi: 10.1212/NXI.0000000000001152. Print 2022 May. PMID: 35260470

Wang Q, Chen K, Su Y, Reiman EM, Dudley JT, Readhead B. Deep learning-based brain transcriptomic signatures associated with the neuropathological and clinical severity of Alzheimer's disease. *Brain Commun*. 2021 Dec 14;4(1):fcab293. doi: 10.1093/braincomms/fcab293. PMCID: PMC8728025.

Wank AA, Robertson A, Thayer SC, Verfaellie M, Rapcsak SZ, Grilli MD. Autobiographical memory unknown: Pervasive autobiographical memory loss encompassing personality trait knowledge in an individual with medial temporal lobe amnesia. *Cortex*. 2022 Feb;147:41-57. doi: 10.1016/j.cortex.2021.11.013. Epub 2021 Dec 2. PMID: 35007893.

Wardell V, Grilli MD, Palombo DJ. Simulating the best and worst of times: the powers and perils of emotional simulation. *Memory*. 2022 Jun 16:1-14. doi: 10.1080/09658211.2022.2088796. Epub ahead of print. PMID: 35708272.

Wen J, Fu CHY, Tosun D, Veturi Y, Yang Z, Abdulkadir A, Mamourian E, Srinivasan D, Skampardoni I, Singh A, Nawani H, Bao J, Erus G, Shou H, Habes M, Doshi J, Varol E, Mackin RS, Sotiras A, Fan Y, Saykin AJ, Sheline YI, Shen L, Ritchie MD, Wolk DA, Albert M, Resnick SM, Davatzikos C; iSTAGING consortium, ADNI, BIOCARD, and BLSA. Characterizing Heterogeneity in Neuroimaging, Cognition, Clinical Symptoms, and Genetics Among Patients With Late-Life Depression. *JAMA Psychiatry*. 2022 May 1;79(5):464-474. doi: 10.1001/jamapsychiatry.2022.0020. PMID: 35262657

Wennström M, Janelidze S, Nilsson KPR; Netherlands Brain Bank, Serrano GE, Beach TG, Dage JL, Hansson O. Cellular localization of p-tau217 in brain and its association with p-tau217 plasma levels. *Acta Neuropathol Commun*. 2022 Jan 6;10(1):3. doi: 10.1186/s40478-021-01307-2. PMID: 34991721

Wilson MA. The Y chromosome and its impact on health and disease. *Hum Mol Genet*. 2021 Oct 1;30(R2):R296-R300. doi: 10.1093/hmg/ddab215. PMCID: PMC8490013.

Windsor R, Stewart S, Schmidt J, Mosqueda M, Piras I, Keller SM, Steinmetz B, Borjesson DL, Huentelman M, Khanna C. A potential early clinical phenotype of necrotizing meningoencephalitis in genetically at-risk pug dogs. *J Vet Intern Med*. 2022 Jul;36(4):1382-1389. doi: 10.1111/jvim.16444. Epub 2022 May 27. PMCID: PMC9308433.

Windsor R, Stewart SD, Talboom J, Lewis C, Naymik M, Piras IS, Keller S, Borjesson DL, Clark G, Khanna C, Huentelman M. Leukocyte and cytokine variables in asymptomatic Pugs at genetic risk of necrotizing meningoencephalitis. *J Vet Intern Med*. 2021 Nov;35(6):2846-2852. doi: 10.1111/jvim.16293. Epub 2021 Oct 23. PMCID: PMC8692191.

Winslow W, McDonough I, Tallino S, Decker A, Vural AS, Velazquez R. IntelliCage Automated Behavioral Phenotyping Reveals Behavior Deficits in the 3xTg-AD Mouse Model of Alzheimer's Disease Associated With Brain Weight. *Front Aging Neurosci*. 2021 Aug 13;13:720214. doi: 10.3389/fnagi.2021.720214. PMCID: PMC8414893.

Winstone JK, Pathak KV, Winslow W, Piras IS, White J, Sharma R, Huentelman MJ, Pirrotte P, Velazquez R. Glyphosate infiltrates the brain and increases pro-inflammatory cytokine TNF α : implications for neurodegenerative disorders. *J Neuroinflammation*. 2022 Jul 28;19(1):193. doi: 10.1186/s12974-022-02544-5. PMCID: PMC9331154.

Wu J, Chen Y, Wang P, Caselli RJ, Thompson PM, Wang J and Wang Y (2022) Integrating Transcriptomics, Genomics, and Imaging in Alzheimer's Disease: A Federated Model. *Front. Radiol*. 1:777030. doi: 10.3389/fradi.2021.777030

Wu J, Dong Q, Gui J, Zhang J, Su Y, Chen K, Thompson PM, Caselli RJ, Reiman EM, Ye J, Wang Y. Predicting Brain Amyloid Using Multivariate Morphometry Statistics, Sparse Coding, and Correntropy: Validation in 1,101 Individuals From the ADNI and OASIS Databases. *Front Neurosci.* 2021 Aug 6;15:669595. doi: 10.3389/fnins.2021.669595. PMID: 348377280.

Wu J, Dong Q, Zhang J, Su Y, Wu T, Caselli RJ, Reiman EM, Ye J, Lepore N, Chen K, Thompson PM, Wang Y. Federated Morphometry Feature Selection for Hippocampal Morphometry Associated Beta-Amyloid and Tau Pathology. *Front Neurosci.* 2021 Nov 25;15:762458. doi: 10.3389/fnins.2021.762458. PMID: 348655732.

Wu J, Zhu W, Su Y, Gui J, Lepore N, Reiman EM, Caselli RJ, Thompson PM, Chen K, Wang Y. Predicting Tau Accumulation in Cerebral Cortex with Multivariate MRI Morphometry Measurements, Sparse Coding, and Correntropy. *Proc SPIE Int Soc Opt Eng.* 2021 Nov;12088:120880O. doi: 10.1117/12.2607169. Epub 2021 Dec 10. PMID: 348710175.

Wu Z, Han Y, Caporaso JG, Bokulich N, Mohamadkhani A, Moayyedkazemi A, Hua X, Kamangar F, Wan Y, Suman S, Zhu B, Hutchinson A, Dagnall C, Jones K, Hicks B, Shi J, Malekzadeh R, Abnet CC, Pourshams A, Vogtmann E. Cigarette Smoking and Opium Use in Relation to the Oral Microbiota in Iran. *Microbiol Spectr.* 2021 Oct 31;9(2):e0013821. doi: 10.1128/Spectrum.00138-21. Epub 2021 Sep 15. PMID: 348557864.

Yang HS, Zhang C, Carlyle BC, Zhen SY, Trombetta BA, Schultz AP, Pruzin JJ, Fitzpatrick CD, Yau WW, Kirn DR, Rentz DM, Arnold SE, Johnson KA, Sperling RA, Chhatwal JP, Tanzi RE. Plasma IL-12/IFN- γ axis predicts cognitive trajectories in cognitively unimpaired older adults. *Alzheimers Dement.* 2022 Apr;18(4):645-653. doi: 10.1002/alz.12399. Epub 2021 Jun 23. PMID: 34160128

Yang Z, Caldwell JZK, Cummings JL, Ritter A, Kinney JW, Cordes D; Alzheimer's Disease Neuroimaging Initiative (ADNI). Sex Modulates the Pathological Aging Effect on Caudate Functional Connectivity in Mild Cognitive Impairment. *Front Psychiatry.* 2022 Apr 5;13:804168. doi: 10.3389/fpsy.2022.804168. eCollection 2022. PMID: 35479489

Yang Z, Nasrallah IM, Shou H, Wen J, Doshi J, Habes M, Erus G, Abdulkadir A, Resnick SM, Albert MS, Maruff P, Fripp J, Morris JC, Wolk DA, Davatzikos C; iSTAGING Consortium; Baltimore Longitudinal Study of Aging (BLSA); Alzheimer's Disease Neuroimaging Initiative (ADNI). A deep learning framework identifies dimensional representations of Alzheimer's Disease from brain structure. *Nat Commun.* 2021 Dec 3;12(1):7065. doi: 10.1038/s41467-021-26703-z. PMID: 34862382

Yang Z, Wu J, Thompson PM, Wang Y. Deep Learning on SDF for Classifying Brain Biomarkers. *Annu Int Conf IEEE Eng Med Biol Soc.* 2021 Nov;2021:1051-1054. doi: 10.1109/EMBC46164.2021.9630850. PMID: 348669623.

Yin F. Lipid Metabolism and Alzheimer's Disease: Clinical Evidence, Mechanistic Link and Therapeutic Promise. *FEBS J.* 2022 Jan 7. PMID: 349259766.

Young CB, Winer JR, Younes K, Cody KA, Betthausen TJ, Johnson SC, Schultz A, Sperling RA, Greicius MD, Cobos I, Poston KL, Mormino EC; Alzheimer's Disease Neuroimaging Initiative and the Harvard Aging Brain Study. Divergent Cortical Tau Positron Emission Tomography Patterns Among Patients With Preclinical Alzheimer Disease. *JAMA Neurol.* 2022 Jun 1;79(6):592-603. doi: 10.1001/jamaneurol.2022.0676. PMID: 35435938

Young DG, Rasheed H, Bleakley A, Langbaum JB. The politics of mask-wearing: Political preferences, reactance, and conflict aversion during COVID. *Soc Sci Med.* 2022 Apr;298:114836. doi: 10.1016/j.socscimed.2022.114836. Epub 2022 Feb 24. PMID: PMC8866197.

Young TL, Scieszka D, Begay JG, Lucas SN, Herbert G, Zychowski K, Hunter R, Salazar R, Ottens AK, Erdely A, Gu H, Campen MJ. Aging influence on pulmonary and systemic inflammation and neural metabolomics arising from pulmonary multi-walled carbon nanotube exposure in apolipoprotein E-deficient and C57BL/6 female mice. *Inhal Toxicol.* 2022 Jan 17:1-15. doi: 10.1080/08958378.2022.2026538. Epub ahead of print. PMID: 35037817.

Yu F, Mathiason MA, Han S, Gunter JL, Jones D, Botha H, Jack C Jr. Mechanistic Effects of Aerobic Exercise in Alzheimer's Disease: Imaging Findings From the Pilot FIT-AD Trial. *Front Aging Neurosci.* 2021 Oct 7;13:703691. doi: 10.3389/fnagi.2021.703691. PMID: PMC8530186.

Zeibich L, Koebele SV, Bernaud VE, Ilhan ZE, Dirks B, Northup-Smith SN, Neeley R, Maldonado J, Nirmalkar K, Files JA, Mayer AP, Bimonte-Nelson HA, Krajmalnik-Brown R. Surgical Menopause and Estrogen Therapy Modulate the Gut Microbiota, Obesity Markers, and Spatial Memory in Rats. *Front Cell Infect Microbiol.* 2021 Sep 30;11:702628. doi: 10.3389/fcimb.2021.702628. PMID: PMC8515187.

Zhang A, Matsushita M, Zhang L, Wang H, Shi X, Gu H, Xia Z, Cui JY. Cadmium exposure modulates the gut-liver axis in an Alzheimer's disease mouse model. *Commun Biol.* 2021 Dec 15;4(1):1398. doi: 10.1038/s42003-021-02898-1. PMID: PMC8674298.

Zhang M, Guo Y, Lei N, Zhao Z, Wu J, Xu X, Wang Y, Gu X. Cortical Surface Shape Analysis Based on Alexandrov Polyhedra. *Proc IEEE Int Conf Comput Vis.* 2021 Oct;2021:14224-14232. doi: 10.1109/iccv48922.2021.01398. PMID: PMC8919730.

Zhang S, Hansen DT, Martin-Garcia JM, Zook JD, Pan S, Craciunescu FM, Burnett JC Jr, Fromme P. Purification, characterization, and preliminary serial crystallography diffraction advances structure determination of full-length human particulate guanylyl cyclase A receptor. *Sci Rep.* 2022 Jul 12;12(1):11824. doi: 10.1038/s41598-022-15798-z.; PMID: PMC9276669.

Zhang W, Andrews-Hanna JR, Mair RW, Goh JOS, Gutchess A. Functional connectivity with medial temporal regions differs across cultures during post-encoding rest. *Cogn Affect Behav Neurosci.* 2022 Jul 27. doi: 10.3758/s13415-022-01027-7. Epub ahead of print. PMID: 35896854.

Zhao J, Lu W, Ren Y, Fu Y, Martens YA, Shue F, Davis MD, Wang X, Chen K, Li F, Liu CC, Graff-Radford NR, Wszolek ZK, Younkin SG, Brafman DA, Ertekin-Taner N, Asmann YW, Dickson DW, Xu Z, Pan M, Han X, Kanekiyo T, Bu G. Apolipoprotein E regulates lipid metabolism and α -synuclein pathology in human iPSC-derived cerebral organoids. *Acta Neuropathol.* 2021 Nov;142(5):807-825. doi: 10.1007/s00401-021-02361-9. Epub 2021 Aug 28. Erratum in: *Acta Neuropathol.* 2021 Nov 1. PMID: PMC8500881.

Zhao X, Ozols AB, Meyers KT, Campbell J, McBride A, Marballi KK, Maple AM, Raskin C, Mishra A, Noss SM, Beck KL, Khoshaba R, Bhaskara A, Godbole MN, Lish JR, Kang P, Hu C, Palner M, Overgaard A, Knudsen GM, Gallitano AL. Acute sleep deprivation upregulates serotonin 2A receptors in the frontal cortex of mice via the immediate early gene *Egr3*. *Mol Psychiatry.* 2022 Mar;27(3):1599-1610. doi: 10.1038/s41380-021-01390-w. Epub 2022 Jan 10. PMID: PMC9210263.

Zhou W, Succar B, Murphy DP, Ashouri Y, Chou YH, Hsu CH, Rapcsak S, Trouard T. Carotid Intervention Improves Cognitive Function in Patients With Severe Atherosclerotic Carotid Disease. *Ann Surg*. 2022 Sep 1;276(3):539-544. doi: 10.1097/SLA.0000000000005555. Epub 2022 Jun 27. PMID: PMC9387545.

Zhou Y, Chawla MK, Rios-Monterrosa JL, Wang L, Zempare MA, Hruba VJ, Barnes CA, Cai M. Aged Brains Express Less Melanocortin Receptors, Which Correlates with Age-Related Decline of Cognitive Functions. *Molecules*. 2021 Oct 16;26(20):6266. doi: 10.3390/molecules26206266. PMID: PMC8541441.



2021 – 2022
Current & Pending Grants

2021-2022 Current Grants

<p>Ali Bilgin (Co-I) NIH/NIA 1U19AG065169-01A1 (Barnes) Precision Aging Network: Closing the Gap Between Cognitive Healthspan and Human Lifespan</p>	<p>09/30/2021-08/31/2026 \$59,988,951 Total Project</p>
<p>Ali Bilgin (Co-I) NIH/NCI 3R01CA245920-03S1 (Altbach/Martin) Advancing MRI Technology for Early Diagnosis of Liver Metastases</p>	<p>12/01/2019-11/30/2024 \$2,342,100 Total Project</p>
<p>Ali Bilgin (Co-PI) CTR056039 (Altbach/Bilgin) Arizona Biomedical Research Commission Development of MRI Biomarkers for Improved Risk Stratification of Patients with Carotid Atherosclerosis to Prevent Stroke</p>	<p>07/01/2021-06/30/2023 \$749,901 Total Project</p>
<p>Alireza Atri (Co-I) NIH via Indiana University 5U01AG057195 (Apostolova) Early Onset AD Consortium - the LEAD Study (LEADS) – Social Worker Funds</p>	<p>06/01/2021 – 05/31/2022 \$31,370</p>
<p>Alireza Atri (Co-I) Alzheimer’s Association via USC (Raman) SG-22-877415-AHEAD CTC AHEAD Alzheimer's Association Proposal: Diverse Recruitment Component</p>	<p>04/01/2022 – 03/31/2023 \$150,000</p>
<p>Alireza Atri (Co-I; BSHRI Site PI) 5P30AG019610-21 (Reiman) NIH/NIA via Arizona State University Arizona Alzheimer’s Disease Research Center – Brain Imaging and Fluid Biomarkers Core</p>	<p>07/01/2020-06/30/2023 \$8,948,605 Total Project</p>
<p>Alireza Atri (Co-PI) Gates Ventures via Banner Alzheimer’s Foundation Resources for the Diagnostic and Prognostic Validation of Blood-Based Biomarkers of Alzheimer’s Disease, Parkinson’s Disease and Related Disorders</p>	<p>09/01/2020-08/31/2024 \$3,085,720 Total Project</p>
<p>Alireza Atri (Core Co-Leader; Co-I) P30AG072980 (Reiman) NIH/NIA via Arizona State University Arizona Alzheimer’s Disease Research Center – Clinical Core</p>	<p>09/05/2021-06/30/2026 \$4,300,085 Total Project</p>
<p>Alireza Atri (Core Co-Leader; Co-I) P30AG072980 (Reiman) NIH/NIA via Arizona State University Arizona Alzheimer’s Disease Research Center – Biomarker Core</p>	<p>09/05/2021-06/30/2026 \$4,984,211 Total Project</p>

Alireza Atri (Project Co-I) Arizona Alzheimer's Consortium via Arizona DHS (Alexander) Clinicopathological Correlates of Rapidly Progressive Alzheimer's Disease	07/01/2021-06/30/2022 \$30,000
Alireza Atri (Project Co-I) Arizona Alzheimer's Consortium via Arizona DHS (Choudhury) Motor Trajectories in neuropathologically-confirmed Lewy Body Disease and other Alzheimer disease and related disorders (ADRD)	07/01/2021 – 06/30/2022 \$45,000
Alireza Atri (Project Co-I) Arizona Alzheimer's Consortium via Arizona DHS (Goldfarb) Mild Behavioral Impairment, MBI: Clinicopathological Characterization, Correlations and Course	07/01/2021 – 06/30/22 \$45,000
Alireza Atri (Project PI) Arizona DHS via Arizona Alzheimer's Consortium Enhancing Clinical and Biological Characterization of The Longevity Cohort Study: Global Staging and Biospecimen Banking	07/01/2021-06/30/202 \$145,000
Alireza Atri (Site PI) U24AG057437 (Aisen) NIH/NIA via University of Southern California Alzheimer's Clinical Trial Consortium	12/02/2017-11/30/2022 \$896,667 Total Project
Alireza Atri (Site PI) R01AG053798 (Aisen) NIH/NIA via University of Southern California Global Alzheimer's Platform Trial-Ready Cohort for Preclinical/Prodromal Alzheimer's Disease	05/01/2019-04/30/2023 \$60,000 Total Project
Andrew Hooyman (PI) F32 AG071110 (Hooyman) NIH/NIA Using an Online Video Game to Predict Functional and Cognitive Decline within the MindCrowd Electronic Cohort	01/01/2022-12/31/2024 \$211,182 Total Project
Aneta Kielar (PI) Innovation in Healthy Aging Treatment of language in Alzheimer's Disease (AD) combining behavioral therapy with noninvasive neuromodulation informed by measures of neural responsiveness	5/42022-4/30/2023 \$63,500 Total Project
Aneta Kielar (PI) Data Science Academy via University of Arizona Stimulating Language in Alzheimer's Dementia by Combining Noninvasive Neuromodulation and Language Therapy Informed by Multimodal Measures of Neurodynamics	1/15/2022-6/2023 \$27,389.25 Total Project

Ann Revill (PI) NIH R15 REAP R15HL148870 Cholinergic Modulation of XII Motoneurons and XII Premotoneurons	07/20/2020-06/30/2023 \$447,700 Total Project
Ann Revill (PI) NIH PRIDE AIRE Effects of Chronic Intermittent Hypoxia on Cholinergic Modulation of Hypoglossal Motoneurons	01/01/2021-12/31/2021 \$159,900 Total Project
Ashley Stokes NIH/NCI/Mayo Clinic Arizona U01CA220378 (Swanson) Quantifying Multiscale Competitive Landscapes of Clonal Diversity in Glioblastoma	09/12/2017-08/31/2022 \$4,062,550
Ashley Stokes NIH/NCI UG3CA247606 (Quarles) Structural and Functional Imaging for Therapy Response Assessment in Brain Cancer	04/01/2020-03/31/2025 \$712,019
Ashley Stokes NIH/NCI R01CA158079 (Quarles) Establishing the validity of brain tumor perfusion imaging	07/01/2017-06/30/2026 \$1,103,708
Ashley Stokes NIH/NIA/University of Arizona R01AG070987 (Weinkauf) Extracranial Carotid Atherosclerosis Contributions to Cognitive Impairment and Alzheimer's Disease Risk	07/1/2021 – 06/30/2026 \$2,773,155
Ashley Stokes AZ Alz Research Consortium/ Barrow Neurological Foundation (Prigatano) Diagnostic and Potential Prognostic Value of Finger Tapping Abnormalities in Assessing Older Adults with Memory Complaints	07/01/2020-06/30/2022 \$165,151
Ashley Stokes (Co-PI) Valley Research Partnership P2-5021 A Highly Specific Inhibitor of Matrix Metalloproteinase-9 Abrogates Tissue Plasminogen Activator Mediated Hemorrhagic Transformation in Experimental Ischemic Stroke	07/2020 – 06/2023 \$50,000 Total Project
Ashley Stokes (Co-PI) Valley Research Partnership (Saleem/Stokes) A Highly Specific Inhibitor of Matrix Metalloproteinase-9 Abrogates Tissue Plasminogen Activator Mediated Hemorrhagic Transformation in Experimental Ischemic Stroke	07/2020-06/2022 \$50,000
Ashley Stokes (PI) NIH/NINDS R01NS124575 (Stokes) Multi-scale functional connectivity in preclinical models of Parkinson's disease	01/01/2022 – 11/30/2026 \$1,996,900 Total Project

Ashley Stokes (PI) NIH/NINDS R21NS125535 Investigating the role of cerebral perfusion in demyelination and repair in multiple sclerosis with MRI	06/01/2022 – 05/31/2024 \$421,958 Total Project
Ashley Stokes (Site PI) NIH/NCI R01CA158079 (Quarles) MRI Assessment of Tumor Perfusion, Permeability and Cellularity	09/16/2011 – 07/31/2021 \$1,897,540 Total Project
Benjamin Readhead NIH R01AG062500 (Velazquez) S6K1 as a novel link between aging and Alzheimer's disease	04/15/2019-02/29/2024 \$3,040,398
Benjamin Readhead NIH P30AG019610 (Reiman) Arizona Alzheimer's Disease Core Center	08/15/2016-06/30/2022 \$13,001,888
Benjamin Readhead (Co-I) NIH P30AG072980 (Reiman) Arizona Alzheimer's Disease Research Center	09/05/2021-06/30/2026 \$15,727,544
Benjamin Readhead (Co-PI) Banner Alzheimer's Institute/NOMIS 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 Alzheimer's and Aging Brain	07/01/2017 – 12/31/2022 \$954,215
Benjamin Readhead (PI) The Benter Foundation 2019-26 Characterizing the microbiome of preclinical and early stage Alzheimer's disease and additional neurodegenerative diseases	09/01/2019-09/01/2022 \$600,000
Benjamin Readhead (PI) Icahn School of Medicine at Mt. Sinai/NIH 0255-4523-4609 Integrated understanding of complex viral network biology in Alzheimer's Disease	03/01/2019-02/28/2022 \$277,372
Benjamin Readhead (PI) University of Washington/NIH UWSC11621 Modulation of Alzheimer's disease by Herpes simplex virus infection	09/01/2019-05/31/2024 \$97,882
Benjamin Readhead (PI) Global Lyme Alliance An interesting necroptosis angle: tick-borne disease and AD	05/10/2019-05/10/2022 \$75,000

Benjamin Readhead (PI) NIH U01AG061835 Identification of the genetic and transcriptomic networks of cognitive and neuropathological resilience to Alzheimer's disease associated viruses	09/01/2018-08/31/2023 \$5,721,083
Carol A Barnes NIH/NIA U19 AG065169 Precision Aging Network: Closing the Gap Between Cognitive Healthspan and Human Lifespan	9/20/2021-6/30/2026 \$59,988,951 Total Cost
Carol A Barnes NIH/NIA R01 AG072643 NPTX2: Preserving Memory Circuits in Normative Aging and Alzheimer's Disease	5/1/2021-4/30/2026 \$5,719,524 Total Cost
Carol A Barnes NIH T32 AG044402 Postdoctoral Training, Neurobiology of Aging and Alzheimer's Disease	5/1/2022-4/31/2027 \$1,455,971 Total Cost
Carol A Barnes (Co-I) Arizona Alzheimer's Consortium (Cowen) High-density neural ensemble recording from hippocampus in behaving aged and young rats during a spatial sequential memory task.	07/1/2022-06/30/2023 \$32,229 Total Project
Carol A Barnes (Co-I) Arizona Alzheimer's Consortium (Hutchinson) An analysis of high-resolution <i>ex vivo</i> MRI from aging macaque brains to estimate white matter and microstructural parameters and to align histological atlases with MRI images	07/1/2022-06/30/2023 \$30,062 Total Project
Carol A Barnes (PI) NIH/NIA R01 AG003376 Neurobehavioral Relations in Senescent Hippocampus	9/30/2021-5/31/2023 \$4,821,974 Total Cost
Christine Belden NIH/NINDS R01NS118669 (Beach) Blinded Comparison of Different Alpha-Synuclein Seeding Assays as Cutaneous Biomarkers of Lewy Body Dementias	08/15/21 – 04/30/25 \$3,195,450 Total Project
Christine Belden AZ DHS via the Arizona Alzheimer's Consortium (AAC) Enhancing Clinical and Biological Characterization of The Longevity Cohort Study: Global Staging and Biospecimen Banking	07/01/21 – 06/30/22 \$110,000

Christine Belden (Co-I) P30AG072980 NIH/NIA via Arizona State University Arizona Alzheimer's Disease Research Center – Clinical Core	09/01/2021-06/30/2026 \$4,300,085 Total Project
Craig Weinkauf (PI) NIH/NIA 1R01AG070987 Extracranial Carotid Atherosclerosis Contributions to Cognitive Impairment and Alzheimer's Disease Risk	8/15/2021-5/31/2026 \$4,900,636 Total Cost
Danielle Goldfarb (Co-I) NIH/NIA via ASU P30AG072980 (Reiman) Arizona Alzheimer's Disease Research Center – Biomarker Core	09/05/2021-06/30/2026 \$4,984,211 Total Project
Danielle Goldfarb (Project PI) Arizona Alzheimer's Consortium via Arizona DHS Mild Behavioral Impairment, MBI: Clinicopathological Characterization, Correlations and Course	07/01/2021-06/30/2022 \$45,000
David Brafman (PI) NIH R21 AG075612-01 Elucidating the protective effects of the KL-VS variant using isogenic hiPSCs	02/01/2022-01/31/2024
David Brafman (PI) Edson Foundation New Idea Award Using CRISPR-based genome approaches to investigate the interactions between APOE and CLU risk variants	02/01/2022-01/31/2023
David Brafman (PI) Alzheimer's Association, AARG-21-851005 Investigating African American-specific ABCA7 variants using hiPSCs	10/01/2021-10/01/2024
David Brafman (PI) NIH/NIA, R21 AG07040 Using hiPSCs to investigate the protective mechanisms of the ApoE4 mutation	09/30/2021-08/31/2023 \$431,750 Total Project
David Brafman (PI) Glen Swette Memorial Funds Swette Young Investigator in ALS	04/09/2020-03/21/2024
David Brafman (PI) Department of Defense, T0042-C Biomanufacturing of Cells in the Neuroectoderm Fate Space	05/01/2018-08/31/2022

David Brafman (PI) NIH/NIGMS, GM121698 Investigating the mechanisms of a multi-state model of Wnt signaling	04/01/2017-03/31/2023
David Raichlen NIH U19AG057377 (Promislaw) Development of Cognitive and Physical Activity Biomarkers for a Companion Dog Model of Alzheimer's Disease	07/2020-06/2022 \$82,343
David Raichlen NIH/NIA P30AG072980 (Reiman) Arizona Alzheimer's Disease Research Center	09/2021 – 06/2026 \$123,750
David Raichlen NIH/NIA/USC R01AG072445 (Raichlen/Alexander/Klimentidis) Inactivity, Sedentary Behavior, and the Risk for Alzheimer's Disease in Middle Aged to Older Adults	04/01/22-03/31/27 \$3,358,131
David Raichlen (PI) NIH/NIA R56AG067200 (Alexander/Raichlen) Physical Activity Predictors of Cognitive and Brain Health in the Risk for Alzheimer's Disease	09/2020-08/2022 \$54,087
David Shprecher (Co-I) NIH/NINDS 1R01 NS118669-01 (Beach) Blinded Comparison of Different Alpha-Synuclein Seeding Assays as Cutaneous Biomarkers of Lewy Body Dementias	07/01/2021–06/30/2025 \$3,195,450 Total Project
David Shprecher (Project PI) Arizona DHS via Arizona Alzheimer's Consortium Establishing a network for prodromal synucleinopathy research in Arizona	07/01/2021-06/30/2022 \$45,000
David W. Coon (Co-I) 1862894-38-C-20 (Underiner) National Endowment for the Arts Creative Health Collaborations Hub	7/1/2020 – 6/30/2022 \$125,000
David W. Coon (Co-I) NIH P30 AG072980 (Reiman) Arizona Alzheimer's Disease Core Center	9/5/2021 – 6/30/2022 \$3,128,303
David W. Coon (Co-I) NIH via University of Arizona 636487 (Barnes) Precision Aging Network: Closing the Gap Between Cognitive Healthspan and Human Lifespan	9/30/2021-8/31/2026 \$313,060

David W. Coon (Co-I) Alzheimer's Association FP00032664 (Byrd) Cognitive Decline and Dementia Risk in Older African Americans	1/1/2022-12/31/2024 \$45,983
David W. Coon (Co-PI) SPA00002017; 3032709; PO 500933462-0-SERV Dignity Health-St. Joseph's Hospital: Barrow Neurological Institute (BNI) Parkinson's Partners in Care: Focus Group and Pilot	1/1/2019 – 6/30/2022 \$181,816
David W. Coon (PI) NIH R01 AG049895 (Coon) EPIC: A Group-based Intervention for Early-stage AD Dyads in Diverse	5/15/2016 – 4/30/2023 \$2,202,742
David Weidman (Co-I) NIH R42AG053149 via MS Technologies (Lure) Multi-Modality Image Data Fusion and Machine Learning Approaches for Personalized Diagnostics and Prognostics of MCI due to AD	01/01/2021-08/31/2022 \$237,162 Total Project
David Weidman (Co-I) NIH/NIA via ASU P30AG072980 (Reiman) Arizona Alzheimer's Disease Research Center – Clinical Core	07/01/2021-06/30/2026 \$4,300,085 Total Project
David Weidman (Project PI) Arizona DHS via Arizona Alzheimer's Consortium Native American Outreach, Recruitment, and Retention Program	07/01/2021-06/30/2022 \$25,000
David Weidman (Site PI) NIH/NIA via USC (ATRI) U24 AG057437 (Aisen) Alzheimer's Clinical Trial Consortium	02/24/2020-11/30/2022 \$896,667 Total Project
David Weidman (Site PI) NIH/NIA via USC (ATRI) R01 AG053798 (Aisen) Global Alzheimer's Platform Trial-Ready Cohort for Preclinical/Prodromal Alzheimer's Disease	05/01/2019-04/30/2023 \$60,000 Total Project
Delrae Eckman (PI) ADHS 17-00007401 Arizona Department of Health Services through the Arizona Biomedical Research Commission Cerebrovascular Dysfunction and Cognitive Decline in Aging APOE2, APOE3 and APOE4 Targeted-Replacement Mice	04/01/2018-03/31/2022 \$225,000 Total Project
Diego Mastroeni Arizona Alzheimer's Consortium: The Effect of Amyloid Precursor Protein Processing on the Alzheimer's Intestinal Flora, a Combinatory Meta-Analysis.	2021-2022 \$60,000

Diego Mastroeni (Co-PI) Department of Defense Probing the Mechanistic Role of Vascular Dysfunction and Vascular Inflammation in TBI-Mediated Cognitive Dysfunction	2018-2022 \$1,200,000
Diego Mastroeni (Co-PI) NOMIS Foundation/Banner Health Public Resource of RNA Sequencing Data from Different Human Brain Cells	2018-2023 \$624,000
Diego Mastroeni (PI) Alzheimer's Association AARGD-17-529197 Gender Effects on identified cell population in Alzheimer's Disease	2018-2022 \$150,000
Diego Mastroeni (PI) BRelN: Resource for Human data, Netherlands.	2019-2025 \$244,000
Diego Mastroeni (PI) Edson Research Award Dysfunctional neuronal mitochondria translocate into neighboring glial cells via tunneling nanotubes.	2021-2022 \$100,000
Don Saner NIH/NIA R01AG055444 (Reiman) Alzheimer's Prevention Initiative ADAD Colombia Trial	04/2017-03/2023 \$14,893,051
Don Saner (Co-I) NIH/NIA R01 AG069453 (Reiman/Su/Chen/Langbaum/Caselli) APOE in the Predisposition to, Protection from and Prevention of Alzheimer's Disease	09/30/2020-03/31/2026 \$27,473,070
Don Saner (Co-I) NIH/NIA R01AG058468 (Reiman/Aisen/Johnson/Langbaum/Sperling/ Tariot) API / A4 Alzheimer's Prevention Trial	09/01/2018-11/30/2024 \$32,005,950 Total Project
Don Saner (Core Co-Leader) NIH/NIA via ASU P30AG072980 (Reiman) Arizona Alzheimer's Disease Research Center – Data Management & Statistics Core	09/05/2021-06/30/2026 \$1,312,710 Total Project
Don Saner (Data Science Sr. Director (IT/EHR Lead)) OT2 OD026549 (Kraft/Moreno/Reiman/Theodorou) NIH via University of Arizona University of Arizona-Banner Health Precision Medicine Initiative Cohort Enrollment Center	04/01/2018-03/31/2023 \$4,761,627

Don Saner (Project PI) Arizona DHS via Arizona Alzheimer's Consortium 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	07/01/2021-06/30/2022 \$50,000
Dona Locke (Co-I) ADHS12-010553 (Caselli) Arizona Department of Health Services Normal and Pathological Aging (Preclinical Alzheimer's Disease	07/01/21-06/30/22
Dona Locke (Co-I) P01 (Reiman/Caselli) Alzheimer's Disease Research Center	07/01/21-06/30/26
Dona Locke (PI) Ralph C. Wilson Foundation Development Fund HABIT Registry	09/01/17-Present
Elizabeth Hutchinson (Co-I) NIH/NIA via Loma Linda University Medical Center R01 AG073230 (Pires, Subaward) Role of Endothelial K+ Channels in Age-Related Dementia	07/01/2014-06/30/2021 \$23,750 Total Subaward
Elizabeth Hutchinson (PI) NIH/NIA R03 780250 (Hutchinson) Microstructural MRI microscopy of post-mortem specimens to identify and improve markers of Alzheimer's Disease pathology	4/1/2021- 03/31/2023 \$161,530 Total Project
Elizabeth Hutchinson (PI) Arizona Alzheimer's Consortium (Hutchinson) An analysis of high-resolution <i>ex vivo</i> MRI from aging macaque brains to estimate white matter and microstructural parameters and to align histological atlases with MRI images	07/1/2022-06/30/2023 \$30,062 Total Project
Elizabeth Hutchinson (PI) Bio5 RAPID Award (Hutchinson) Low intensity pulsed ultrasound induction of neuronal regeneration following traumatic brain injury.	1/14/2022-7/31/2022 \$48,437 Total Project
Emily Cope (PI) NIH/NIAID R15AI147148 (Cope and Caparaso, MPI) Determining the Role of the Upper and Lower Airway Microbiota as Drivers of Concomitant Inflammatory Responses in patients with Chronic Rhinosinusitis and Asthma.	07/01/2019-06/30/2023 \$468,472 Total Project
Emily Cope (PI) CTR057001 (Cope) Arizona Alzheimer's Consortium Alzheimer's /AZDHS Arizona Statewide Alzheimer's Research	07/01/2021-06/30/2022 \$150,000 Total Project

Emily Cope (PI) NIH/NIA R21AG074203 (Cope) Development of in vivo quantitative stable isotope probing to quantify microbiome dynamics in Alzheimer's disease	09/01/2021-08/31/2023 \$418,000 Total Project
Eric Reiman Eli Lilly and Company TRAILBLAZER-ALZ3	07/01/2021 – 06/30/2027 \$4,116,286
Eric Reiman (Co-I) NIH/NIA R01 AG069453 (Reiman/Caselli/Su/Chen/Langbaum) APOE in the Predisposition to, Protection from and Prevention of Alzheimer's Disease	10/01/2020-03/31/2026 \$27,473,070 Total Project
Eric Reiman (Co-I) U19 AG024904 (Weiner) NIH/NIA via Northern California Institute Res & Educ. Alzheimer's Disease Neuroimaging Initiative	08/01/2017-07/31/2022 \$400,000 Total Project
Eric Reiman (Co-I) NIH via USC P01AG052350 (Zlokovic/Toga) Vascular Contributions to Dementia and Genetic Risk Factors for Alzheimer's Disease	05/01/2022-03/31/2027 \$1,015,500 Total Project
Eric Reiman (Co-I) VCID-17-209279 (Zlokovic) Alzheimer's Association via USC Vascular Contributions to Dementia and Amyloid and Tau Lesions in APOE4 Carriers (VCID)	03/01/2020-02/28/2023 \$322,898 Total Project
Eric Reiman (Co-I) NIH/NIA via University of Washington U24AG072122 (Kukull) National Alzheimer's Coordinating Center	07/01/2021 – 05/31/2026 \$133,900 Total Project
Eric Reiman (Co-I) NIH/NIA via MGH R01AG054671 (Quiroz) Relationship between tau pathology and cognitive impairment in autosomal dominant Alzheimer's disease	09/01/2017-05/31/2022 \$208,812 Total Project
Eric Reiman (Co-I) 1R01AG070883 (Bendlin/Kind) NIH/NIA via University of Wisconsin-Madison The Neighborhoods Study: Contextual Disadvantage and Alzheimer's Disease and Related Dementias	03/01/2021-02/28/2026 \$264,852 Total Project
Eric Reiman (Co-I) U54MD000507 (Manson/Buchwald) NIH/NIMHH via University of Colorado Denver American Indian and Alaska Native Health Disparities	09/22/2017-04/30/2022 \$98,067 Total Project

Eric Reiman (Co-I) NIH/NIA RF1AG0733424 (Su) Tracer harmonization for amyloid and tau PET imaging using statistical and deep learning techniques	08/01/2022-07/31/2025 \$2,282,378 Total Project
Eric Reiman (Co-I) NIH/NIA via University of Arizona OT2HL161847 (Nikolich-Zugich) Researching COVID To Enhance Recovery (RECOVER) Initiative	05/2021-05/2025 \$881,958
Eric Reiman (Co-PI) Gates Ventures via Banner Alzheimer's Foundation Resources for the Diagnostic and Prognostic Validation of Blood-Based Biomarkers of Alzheimer's Disease, Parkinson's Disease and Related Disorders	09/01/2020-08/31/2024 \$3,085,720 Total Project
Eric Reiman (PI) NIH/NIA via ASU P30AG019610 (Reiman) Arizona Alzheimer's Disease Core Center	07/01/2016-06/30/2023 \$12,516,208 Total Project
Eric Reiman (PI) NIH/NIA R01AG055444 (Reiman/Tariot/Lopera) Alzheimer's Prevention Initiative ADAD Colombia Trial	04/01/2017-03/31/2023 \$14,893,051 Total Project
Eric Reiman (PI) NIH/NIA R01AG058468 (Reiman/Aisen/Johnson/Langbaum/Sperling/Tariot) API / A4 Alzheimer's Prevention Trial	09/01/2018-11/30/2024 \$32,005,950 Total Project
Eric Reiman (PI) U01NS093334 (Stern/Cummings/Reiman/Shenton) NIH/NINDS via Boston University/Mayo Clinic Chronic Traumatic Encephalopathy: Detection, Diagnosis, Course and Risk Factors	12/15/2015-11/30/2022 \$281,796 Total Project
Eric Reiman (PI) OT2 OD026549 (Kraft/Moreno/Reiman/Theodorou) NIH via University of Arizona University of Arizona-Banner Health All of Us Research Program	04/01/2018-03/31/2023 \$2,655,634 Total Project
Eric Reiman (PI) NOMIS Foundation (Reiman/Liang/Beach/Readhead/Dudley) 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	09/01/2007-12/31/2022 \$5,000,000 Total Project

Eric Reiman (PI) NIH/NIA via ASU P30AG072980 Arizona Alzheimer's Disease Research Center	09/01/2021-06/30/2026 \$15,077,717 Total Project
Fei Yin (Co-I) NIH/NIA via FIU R21AG072561 (Gu/Jentarra) Targeting Whole-body Fatty Acid Metabolism in Alzheimer's Disease, with Special Interest in Lauric acid	06/01/2021-05/31/2023 \$76,750 Total Project
Fei Yin (Co-I) NIH/NIA R01AG057931 (Brinon/Mosconi/Chang) Sex Differences in the Molecular Determinants of Alzheimer's Disease Risk: Prodromal Endophenotype	05/15/2018-03/31/2023 \$6,006,958 Total Project
Fei Yin (Co-I) NIH/NIA R37AG053589 (Brinton) Aging and Estrogenic Control of the Bioenergetic System in Brain	04/15/2022-03/31/2027 \$2,686,250 Total Project
Fei Yin (Co-I) NIH/NIA via Duke University RF1AG057931 (Kaddurah-Daouk/Brinton/Kastenmuller/Chang) Metabolic Networks and Pathways Predictive of Sex Differences in AD Risk and Responsiveness to Treatment	08/01/2018-03/31/2023 \$640,519 Total Project
Fei Yin (Co-I) NIH/NIA RF1AG067771 (Thatcher) Novel Allosteric Activation of Nicotinamide Rescue	09/01/2020-08/31/2023 \$2,264,368 Total Project
Fei Yin (Co-I) NIH/NIA U01AG076450 (Thatcher) Nonlipogenic ABCA1 inducers for ADRD	07/01/2022-06/30/2027 \$3,799,050 Total Project
Fei Yin (Core Leader) NIH/NIA P01AG026572 (Brinton) Perimenopause in Brain Aging and Alzheimer's Disease Analytic Core	04/01/2021-05/31/2026 \$15,168,816 Total \$2,282,929 Analytic Core
Fei Yin (PI) NIH/NIA RF1AG068175 (Yin) ApoE Regulation of Neuron-Astrocyte Metabolic Coupling in Alzheimer's Disease	05/15/2021-04/30/2024 \$1,131,312 Total Project
Garilyn Jentarra (Co-PI) NIH 7R21AG072561-02 Targeting Whole Body Fatty Acid Metabolism in Alzheimer's Disease, with Special Interest in Lauric Acid	08/09/2021-05/31/2023 \$459,771 Total Project

Garilyn Jentarra (PI) AZ Dept of Health Services-Arizona Alzheimer's Consortium Identification and Culture of Microbes in Brain Tissue from Alzheimer's Disease Patients and Controls	07/01/2021-06/30/2022 \$60,000 Total Project
Geidy Serrano NIH/University of Arizona R01AG072643 (Barnes) NPTX2: Preserving memory circuits in normative aging and Alzheimer's Disease	04/2021-03/2026 \$40,875
Geidy Serrano (Co-I) NIH/NIA via ASU 3P30AG019610-20S1 (Reiman) Arizona Alzheimer's Disease Research Center - Presence and Neuropathological Consequences of CNS Covid-19 in Consecutive Autopsies During the Worldwide Pandemic.	07/01/2020-06/30/2023 \$386,476 Total Project
Geidy Serrano (Co-I) NIH/NINDS R01NS118669-01 (Beach) Blinded Comparison of Different Alpha-Synuclein Seeding Assays as Cutaneous Biomarkers of Lewy Body Dementias	07/01/2020-06/30/2025 \$3,195,450 Total Project
Geidy Serrano (Co-I) NIH/NIA via ASU P30AG072980 (Reiman) Arizona Alzheimer's Disease Research Center – Biomarker Core	09/05/2021-06/30/2026 \$4,984,211 Total Project
Geidy Serrano (Co-PI) Gates Ventures via Banner Alzheimer's Foundation Resources for the Diagnostic and Prognostic Validation of Blood-Based Biomarkers of Alzheimer's Disease, Parkinson's Disease and Related Disorders	09/01/2020-08/31/2024 \$3,085,720 Total Project
Geidy Serrano (Core Co-Leader; Co-I) NIH/NIA via ASU P30AG072980 (Reiman) Arizona Alzheimer's Disease Research Center – Neuropathology Core	09/05/2021-06/30/2026 \$1,636,000 Total Project
Geidy Serrano (PI) Astrocyte Biology in PD Grant ID 17901 Michael J. Fox Foundation for Parkinson's Research Characterization of isolated human astrocyte population in aging and Lewy body pathology	10/01/2019-01/05/2022 \$148,395 Total Project
Geidy Serrano (Project PI) Arizona Alzheimer's Research Consortium Patient-based postmortem fibroblast banking for translational research	07/2021-06/2022 \$115,000

Geidy Serrano (Project PI) Arizona Alzheimer's Research Consortium A Human Brain Single-Cell Suspension Resource	07/2021-06/2022 \$190,000
Gene E. Alexander (Co-I) NIH/NIA R01AG070987 (Weinkauf) Extracranial Carotid Atherosclerosis Contributions to Cognitive Impairment and Alzheimer's Disease Risk	8/15/21-5/31/26 \$4,900,635 Total Cost
Gene E. Alexander (Co-I) NIH/NIA R01AG054077 (MPIs: Woods, Cohen, Marsiske) Augmenting Cognitive Training in Older Adults	9/1/16 – 4/30/23 \$1,474,342 Total Cost
Gene E. Alexander (Co-I) McKnight Brain Research Foundation (Williamson) Transcutaneous Vagal Nerve Stimulation and Cognitive Training to Enhance	10/1/19-9/30/22 \$30,000 Total Cost
Gene E. Alexander (Co-I) NIH/NIA R01AG061888 (Wilson) Evaluating the Neurocomputational Mechanisms of Explore-Exploit Decision Making in Older Adults	9/1/19-8/31/24 \$1,765,250 Total Cost
Gene E. Alexander (Co-I) NIH/NIA R01AG062543 (Chou) Enhancement of Hippocampal Plasticity Using Repetitive Transcranial Magnetic Stimulation	5/1/20-4/31/25 \$3,546,144 Total Cost
Gene E. Alexander (Core Leader) NIH/NIA 3P30AG019610-19S1 (Reiman) Arizona Alzheimer's Disease Core Center - Brain Imaging and Fluid Biomarkers Core	9/15/18 - 6/30/23 \$3,701,167 Total Cost
Gene E. Alexander (Core Leader) NIH/NIA P30AG072980 (Reiman) Biomarker Core: Arizona Alzheimer's Disease Research Center	9/1/21 - 6/30/26 \$4,984,210 Total Cost
Gene E. Alexander (PI) NIH/NIA R01AG064587 (MPIs: Alexander, Bowers, Woods) Revitalizing Cognition in Older Adults at Risk for Alzheimer's Disease with Near-Infrared Photobiomodulation	8/01/19 – 4/30/24 \$3,797,232 Total Cost
Gene E. Alexander (PI) NIH/NIA R01AG072445 (MPIs: Raichlen, Alexander, Klimentidis) Inactivity, Sedentary Behavior, and the Risk for Alzheimer's Disease in Middle Aged to Older Adults	4/01/21 - 3/31/26 \$3,422,710 Total Cost

Gene E. Alexander (PI) NIH/NIA R56AG067200 (MPIs: Alexander, Raichlen) Physical Activity Predictors of Cognitive and Brain Health in the Risk for Alzheimer's Disease	4/01/21 - 3/31/26 \$767,484 Total Cost
Gene E. Alexander (PI) McKnight Brain Research Foundation (MPIs: Alexander, Bowers, Woods) A Pilot Intervention with Near Infrared Stimulation: Revitalizing Cognition in Older Adults	5/1/18-4/30/23 NCE \$60,000 Total Cost
Gene E. Alexander (PI) State of Arizona Lifestyle/Physical Activity Biomarkers in Brain Aging & Alzheimer's Disease Risk	7/1/11 – 6/30/22 \$48,000 Total Cost
Greg Caporaso (co-I) NIH/NCI 5U54CA143925 (Ingram) The Partnership for Native American Cancer Prevention	09/01/2019-08/31/2024 \$7,582,050 Total Project
Greg Caporaso (co-I) G201912432 (Stachurski) Alfred P Sloan Foundation via Australian National University Document Creation and Publishing Tools for Next-Generation Scientific Textbooks	12/01/2019-10/31/2022 \$210,573 Total Project
Greg Caporaso (co-I) NIH/NIA R21AG074203 (Cope) Development of in vivo quantitative stable isotope probing to quantify microbiome dynamics in Alzheimer's Disease	09/01/2021-04/30/2023 \$418,000 Total Project
Greg Caporaso (co-I) CTR057001 (Cope) Arizona Alzheimer's Consortium/AZDHS Arizona Statewide Alzheimer's Research	07/01/2021-06/30/2022 \$150,000 Total Project
Greg Caporaso (co-I) NIH U54MD012388 (Baldwin) Southwest Health Equity Research Collaborative	07/01/2017-06/30/2022 \$5,174,021 Total Project
Greg Caporaso (co-I) NIH/NIAID R15AI156771 (Pearson) Are Minority Health Disparities in MRSA/MSSA Infections Related to Carriage and Social Relationships?	12/01/2020-11/30/2022 \$418,000 Total Project
Greg Caporaso (co-I) NSF 2125088 (Marks) Discovering in reverse – using isotopic translation of omics to reveal ecological interactions in microbiomes.	09/01/2021-08/30/2026 \$3,000,000 Total Project

Greg Caporaso (PI) NIH/NCI 1U24CA248454-01 (Caporaso) Advanced Development of Informatics Technologies for Cancer Research and Management	07/01/2020-06/30/2025 \$3,798,959 Total Project
Greg Caporaso (PI) 2021-237226 (5022) (Caporaso) Silicon Valley Community Foundation Engaging Native American Students in Scientific Computing w QIIME 2 (EOSS-D&I)	09/01/2021-08/31/2023 \$399,301 Total Project
Greg Caporaso (PI) NIH/NIADI R15AI147801 (Cope) Determining the Role of the Upper and Lower Airway Microbiota as Drivers of Concomitant Inflammatory Responses in patients with Chronic Rhinosinusitis and Asthma	07/01/2019-06/30/2023 \$468,472 Total Project
Heather Bimonte-Nelson (Co-I) NIH/NIA P30 AG019610 (Reiman) Arizona Alzheimer's Disease Core Center	08/15/2016-6/30/2023 \$13,001,885 Total Project
Heather Bimonte-Nelson (Co-I) NIH/NIA P30 AG072980 (Reiman) Arizona Alzheimer's Disease Research Center (ADRC)	09/05/2021-06/30/2026 \$15,727,544 Total Project
Heather Bimonte-Nelson (Co-I) NIH/NINDS R01 NS116657 (Stabenfeldt) Exploiting sex-dependent brain injury response for nanoparticle therapeutics	01/01/2021-11/30/2025 \$3,193,033 Total Project
Heather Bimonte-Nelson (Co-I) NIH/NIDA R01 DA043172 (Olive) Characterization and Reversal of Neurocognitive Dysfunction Produced by Long-term Synthetic Cathinone Use	09/30/2017-07/31/2022 \$1,899,025 Total Project
Heather Bimonte-Nelson (PI) NIH/NIA R01 AG028084 Variations in Hormones During Menopause – Effects on Cognitive and Brain Aging	06/01/2016-05/31/2023 \$2,363,615 Total Project
Heather Bimonte-Nelson (PI) CTR057001 (Coon) Arizona Alzheimer's Consortium/Arizona Dept of Health Services Comparison of Age-related Responses to Menopause Variations on Brain Functioning	07/01/2021-06/30/2022 \$35,000 Total Project
Hillary Protas (Co-I) NIH via MGH 5R01AG054671 (Quiroz) Relationship between tau pathology and cognitive impairment in autosomal dominant Alzheimer's disease	07/01/2017-06/30/2022 \$208,812 Total Project

Hillary Protas (Co-I) NIH/NIA RF1AG073424 (Su) Tracer harmonization for amyloid and tau PET imaging using statistical and deep learning techniques	08/01/2022-07/31/2025 \$2,282,378 Total Project
Hillary Protas (Co-I) NIH/NIA via JHU R01AG059390 (Smith) Longitudinal Molecular Imaging of Neuropathology and Serotonin in Mild Cognitive Impairment	07/01/2020 – 01/31/2023 \$27,891
Hillary Protas (Project Co-I) State of Arizona via Arizona Alzheimer's Research Consortium Advanced Imaging and Machine Learning in Alzheimer's Research	07/01/2021-06/30/2022 \$250,000
Hillary Protas (Project Co-I) State of Arizona via Arizona Alzheimer's Research Consortium Statistical and Neuroimaging Data Science Core Resources Serving the Consortium Members	07/01/2021-06/30/2022 \$80,000
Hillary Protas (Subrecipient Co-I) NIH via NCIRE U19AG024904 (Weiner) Alzheimer's Disease Neuroimaging Initiative	09/30/2017-07/31/2022 \$400,000 Total Project
Ignazio Piras DoD/Mayo Clinic Arizona W81XWH1910534 (Schwedt) A multidisciplinary translational approach to investigate the mechanisms, predictors and prevention of persistent posttraumatic headache	09/01/2019-08/30/2024 \$1,242,656
Ignazio Piras NIH/NIDDK R01DK120890 (DiSefano) Profiling extracellular vesicle cargo in obesity and type 2 diabetes	09/20/2019-07/31/2025 \$3,690,587
Ignazio Piras NIH/Northwestern R01AG067781 (Rogalski) Cognitive SuperAging: A model to explore resilience and resistance to aging and Alzheimer's disease	05/01/2020-01/31/2025 \$397,220
Ignazio Piras NIH/University of Arizona R01AG072643 (Barnes) NPTX2: Preserving memory circuits in normative aging and Alzheimer's Disease	05/01/2021-04/30/2026 \$1,298,796
Ignazio Piras NIH/University of Florida R01AG057764 (Ebner) Uncovering and Surveilling Financial Deception Risk in Aging – Alzheimer's Disease Supplement	07/01/2021-06/30/2022 \$57,992

Ignazio Piras AZ DHS/AARC/Banner Health (Serrano) A Human Brain Single-Cell Suspension Resource	01/01/2022-06/30/2022 \$20,000
Ignazio Piras Foundation (Pirrotte) Evaluation of Ovarian Cancer Biomarkers from Pap smears	01/01/2022-12/31/2022 \$221,061
Jeremy Pruzin (PI) Alzheimer's Association Clinical Scientist Fellowship AACSF-20-685828 Modulation of Imaging Biomarkers by Activity Level and Vascular Risk	04/2020-04/2022 \$138,030
Jeremy Pruzin (Project PI) CTR057001 Arizona Alzheimer's Consortium Pilot Project Award APOE4, Vascular Risk, and AD Biomarkers in PSEN1 E280A Carriers and Controls	07/01/2021-06/30/2022 \$30,000
Jessica Langbaum Eli Lilly and Company TRAILBLAZER-ALZ3	07/2021-06/2027 \$4,116,286
Jessica Langbaum (Co-I) NIH/NIA R01AG055444 (Reiman/Tariot/Lopera) Alzheimer's Prevention Initiative ADAD Colombia Trial	04/01/2017-03/31/2023 \$14,893,051 Total Project
Jessica Langbaum (Co-I) NIH/NIA via USC R01AG061848 (Aisen/Johnson/Sperling) Combination anti-amyloid therapy for preclinical Alzheimer's Disease	09/30/2018-05/31/2025 \$750,000 Total Project
Jessica Langbaum (Core Co-Leader; Co-I) NIH/NIA via ASU P30AG072980 (Reiman) Arizona Alzheimer's Disease Research Center – Administrative Core	09/05/2021-06/30/2026 \$1,836,125 Total Project
Jessica Langbaum (Core Co-Leader; Co-I) NIH/NIA via ASU P30AG072980 (Reiman) Arizona Alzheimer's Disease Research Center – Outreach and Recruitment Core	09/05/2021-06/30/2026 \$381,080 Total Project
Jessica Langbaum (PI) NIH/NIA R01AG058468 (Reiman/Aisen/Johnson/Langbaum/Sperling/ Tariot) API A4 Alzheimer's Prevention Trial	09/01/2018- 11/30/2024 \$32,005,950 Total Project

Jessica Langbaum (PI) NIH/NIA R01 AG063954 (Langbaum/Bleakley) Establishing the science behind Alzheimer's recruitment registries: opportunities for increasing diversity and accelerating enrollment into trials	09/01/2019-06/30/2024 \$8,793,374 Total Project
Jessica Langbaum (PI) NIH/NIA R01 AG063954-02S1 (Langbaum/Bleakley) Establishing the science behind Alzheimer's recruitment registries: opportunities for increasing diversity and accelerating enrollment into trials	09/15/2020-06/30/2022 \$387,949 Total Project
Jessica Langbaum (PI) NIH/NIA R01AG069453 (Reiman/Caselli/Su/Chen/Langbaum) APOE in the Predisposition to, Protection from and Prevention of Alzheimer's Disease	07/01/2020-03/31/2026 \$27,473,070 Total Project
Jessica Langbaum (PI) NIH/NIA R33AG070604 (Langbaum) Optimizing Research Infrastructure of Registries to Accelerate Participant Recruitment into Alzheimer's Focused Studies	08/2021-07/2026 \$3,941,399
Jessica Langbaum (Project PI) Arizona DHS via Arizona Alzheimer's Consortium Alzheimer's Prevention Registry	07/01/2021-06/30/2022 \$15,000
John Fryer (Co-I) NIH R37AI071106 (Kita) Mechanisms of Allergen-induced Type 2 Immunity-Administrative Supplement	11/1/20-4/30/23
John Fryer (Co-I) NIH/NINDS via Mayo Clinic Rochester R01NS122174 (Johnson) Defining MHC class I restricted antigen presentation to CD8 T cells in experimental AD and Tauopathy	07/01/21 – 06/30/2026
John Fryer (PI) NIH/NIA RF1AG06211 (Fryer/Liu) Microglial apoE in neuroinflammation and Alzheimer's disease	08/01/2019-03/31/2024 \$4,000,570
John Fryer (PI) NIH/NIA RF1AG062077 (Fryer/Petrucci) Novel genetic modifiers of C9orf72 and Tau toxicity	08/15/2019-03/31/2024 \$4,037,235
John Fryer (PI) NIH/NIA R56AG062556 (Springer/Fryer) Selective autophagy in Alzheimer's disease and related dementias	08/01/2019-07/31/2021 \$782,049

John Fryer (PI) Coins for Alzheimer's Trust The role of microglial lipid signaling in Alzheimer's disease pathogenesis	2019 – 2021
John Fryer (PI) Cure Alzheimer's Foundation curealz.org The role of Clusterin in tau pathology	02/01/20-01/31/22
John Fryer (PI) Mayo Clinic Alzheimer's Disease Center pilot grant Single-cell/nucleus transcriptional signatures underlying Alzheimer's disease pathology	07/01/19-06/30/22
John Fryer (Project PI) NIH/NINDS U54NS110435 (Ross/Fryer/Chang) Lewy Body Dementia CWOW, Project 1: Omics driven network analysis in LBD	09/20/2019-06/30/2024 \$624,533
Jonathan Lifshitz (Co-PI) GR-ARPA-CACTIS-010122-01 (Handmaker) Governor's Office of Strategic Planning and Budgeting Maricopa County Collaboration on Concussion from Domestic Violence (MC3DV)	01/01/2022 – 12/31/2022 \$248,794 Total Project
Jonathan Lifshitz (PI) U.S. Dept. of Veterans Affairs VA Merit I01 RX002472 Brain Injury Rehabilitation Modality, Regulation, & Structural Plasticity	03/15/2019 – 09/30/2024 \$1,100,000 Total Project
Jonathan Lifshitz (PI) U.S. Dept. of Veterans Affairs VA Merit I01 RX002472 Developing and Testing a Novel Virtual Cognitive Rehabilitation Program to Alleviate Persistent Cognitive Dysfunction Following Traumatic Brain Injury	12/01/2020 – 09/30/2024 \$526,529 Total Project
Jonathan Lifshitz (PI) Neurotrauma Sciences, LLC NCL-TBI-2021-011 Sleep, inflammation and therapeutic efficacy of NTS-104 in diffuse TBI	10/01/2021 – 09/30/2023 \$314,836 Total Project
Joyce Lee-Iannotti (Project PI) Arizona DHS via Arizona Alzheimer's Consortium Pilot Project: Idiopathic REM Behavior Disorder (iRBD) as a Predictor of Neurodegenerative Disease	07/01/2021-06/30/2022 \$30,000
Judith Su (PI) NIH/NIGMS R35GM137988 Label-free single molecule detection for basic science and translational medicine	09/01/2020-08/31/2025 \$1,822,950 Total Project

Judith Su (PI) Defense Threat Reduction Agency 12326236 Sensitive, Selective, and Affordable Chemical Threat Sensing Using Frequency Locked Microtoroid Optical Resonators	08/1/2018-02/28/2023 \$2,160,212 Total Project
Judith Su (PI) Flinn Foundation 26223 Identifying and Detecting Diseases Prior to Physical Presentation of Symptoms	05/01/2019-10/21/2022 \$55,000 Total Project
Judith Su (PI) Cargill, Incorporated 00992519 Measuring Binding Affinities of Ligands to Taste Receptors Using Microtoroid Optical Resonators	010/04/2021-10/03/2022 \$84,597 Total Project
Kendall Van-Keuren Jensen (Co-I) NIH/UCSD 4UH3CA24168 (Laurent) Development and application of a scalable workflow for immunoaffinity isolation and molecular analysis of exRNA carrier subclasses.	09/01/2019 – 08/31/2023 \$466,532
Kendall Van-Keuren Jensen (Co-I) NIH/Massachusetts General Hospital 1UG3TR002878 (Das) Molecular dissection and imaging of extracellular vesicles to define their origin and targets	09/16/2019 – 06/30/2023 \$545,851
Kendall Van-Keuren Jensen (Co-I) Michael J. Fox Foundation/ USC 17047 (Craig) Identification of RNA Isoform and Splicing Based Biomarkers for Parkinson's Disease	10/16/2019 – 10/16/2022 \$225,000
Kendall Van-Keuren Jensen (Co-I) CP18 Foundation (Berens) Immunologic/Transcriptomic Landscape in Glioblastoma Patients	03/01/2021 – 02/28/2023 \$462,384
Kendall Van-Keuren Jensen (Co-I) NIH/SJHMC R21NS116385-01A1 (Medina) Novel knock-in mouse models of ALS and myopathy-linked Matrin 3 mutations	09/01/2020 -05/31/2023 \$73,173
Kendall Van-Keuren Jensen (Co-I) NIH/SJHMC R01NS12331 (Sattler) Microglia contribution to disease pathogenesis in C9orf72 ALS/FTD	09/01/2021 – 08/31/2026 \$1,618,800
Kendall Van-Keuren Jensen (Co-I) NIH/UAB R01AG075059 (Thlacker-Mercer) The essentiality of serine and glycine for skeletal muscle regeneration in aging	01/15/2022 – 11/30/2026 \$210,108

Kendall Van-Keuren Jensen (Co-I) NIH/SJHMC R21NS125861 (Sattler) Astrocyte regulation of cortical neurodegeneration in C9orf72 FTD/ALS	09/2021-03/2023 \$144,000
Kendall Van-Keuren Jensen (Co-I) Flinn Foundation 22-0641 (Von Hoff) Development and Commercialization of a Blood-Based Assay for Disease Monitoring in Patients with Pancreatic Cancer	04/2022 – 09/2023 \$100,000
Kendall Van-Keuren Jensen (Co-I) Nomis Foundation/Banner Health 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	07/2020 – 06/2022 \$907,405
Kendall Van-Keuren Jensen (Multi PI) 1UG3CA241703 (Raffai) NIH/ Northern California Institute for Research and Education P.R.I.S.M: Purification of exRNA by Immuno-capture and Sorting using Microfluidic	09/01/2019 – 08/31/2023 \$569,069
Kendall Van-Keuren Jensen (Multi) Private Foundation (Jensen/Von Hoff) Extra Cellular Vesicles	06/2021 – 08/2022 \$732,506
Kendall Van-Keuren Jensen (PI) Michael J. Fox Foundation MJFF-021142 Correlation of exRNA cargo from brain-enriched extracellular vesicles in blood with single nuclei sequencing from brain.	01/2022 -01/2024 \$546,803
Kendall Van-Keuren Jensen (PI) Michael J. Fox Foundation MJFF-021069 (Jensen) FOUNDIN-PD supplemental funding	03/2022 – 02/2024 \$117,134
Kendall Van-Keuren Jensen (PI) CP20 Foundation Natural Killer Cell-Derived Extracellular Vesicles as Therapeutic and Prognostic Tools in Non-Small Cell Lung Cancer	04/2022 – 03/2024 \$912,250
Layla Al-Nakkash (PI) AZ Dept of Health Services-Arizona Alzheimer's Consortium Reversal of western diet induced Alzheimer's-like pathology with genistein and/or exercise.	07/01/2021-06/30/2022 \$27,000 Total Project

Layla Al-Nakkash (PI) Diabetes Action research & Education Foundation Ability of 12-weeks moderate exercise and/or genistein (soy) to reverse hyperglycemia, hyperinsulinemia, fatty liver disease and microbiome changes induced by chronic consumption of high fat high sugar diet.	01/01/2021-12/30/21 \$10,000 Total Project
Lee Ryan NIH/NIA U19 AG065169 (Barnes) Precision Aging Network: Closing the Gap Between Cognitive Healthspan and Human Lifespan	9/20/2021-6/30/2026 \$59,988,951 Total Cost
Lee Ryan NIH R01AG062543 (Chou) Enhancement of Hippocampal Plasticity Using Repetitive Transcranial Magnetic Stimulation	05/01/2020-4/30/2025 \$735,125 Total Cost
Lee Ryan NIA 3P30AG019610-19S1 (Reiman) Brain Imaging and Fluid Biomarkers (BIFB) Core	09/15/2018-6/30/2022 \$3,701,167 Core Total Cost
Lee Ryan (Co-I) NIH/NIA U01AG066623 Admin Supplement (Hay) IND Enabling Studies for a Novel Mas Receptor Agonist for Treatment of Cognitive Impairment in Patients at Risk for Alzheimer's Disease Related Dementia (Admin Supplement)	4/1/21 – 3/31/23 \$249,769 DC
Lee Ryan (PI) State of Arizona, DHS Grant Evaluating Neurofilament Light Protein as a Marker of Neuronal Damage in Older Adult Survivors of SARS-CoV2	07/01/21 – 06/30/22 \$42,000 Total Cost
Lee Ryan (PI) State of Arizona, DHS Grant Expanding pipelines and data sharing resources for MRI analyses for studies of aging and Alzheimer's disease at the University of Arizona	7/01/2021-6/30/2022 \$92,500 TC
Lee Ryan (PI) State of Arizona, DHS Grant Evaluating Neurofilament Light (NFL) Protein as a Marker of Neuronal Damage in Older and Middle-Aged Adult Survivors of SARS-CoV2	07/01/22 – 06/30/23 \$53,200 Total Cost
Mark Swanson (PI) AZ Dept of Health Services-Arizona Alzheimer's Consortium The Role of Phosphorylation on the Function of the Telomere Protection Protein RAP1	07/01/2021-06/30/2022 \$8,175 Total Project

Matt Huentelman (Co-I) Grant#20170715 (Padilla) Aging Minds Foundation/Baylor White Institute Early Onset Alzheimer's Disease Genomic Study	09/01/2017 – 06/30/2023 \$71,370
Matt Huentelman (Co-I) SOW 33 PO# 67513702 (Vargas) Mayo Clinic, Arizona Characterizing Chemo-Radiotherapy Treatment–related cardiac changes	08/07/2019 –08/01/2022 \$71,255
Matt Huentelman (Co-I) NIH/Rhode Island Hospital UG30D023313 (Deoni) The Developing Brain: Influences and Outcomes	09/21/2016 – 08/31/2023 \$825,338
Matt Huentelman (Co-I) DoD/Mayo Clinic, AZ W81XWH1910534 (Schwedt) A multidisciplinary translational approach to investigate the mechanisms, predictors and prevention of persistent post traumatic headache.	09/01/2019 – 08/31/2023 \$1,247,594
Matt Huentelman (Co-I) NIH/Northwestern University R01 AG067781 (Rogalski) Cognitive SuperAging: A model to explore resilience and resistance to aging and Alzheimer's disease	05/01/2020 – 01/31/2025 \$397,866
Matt Huentelman (Co-I) NIH/University of Arizona R01 AG072643-01 (Barnes) NPTX2: Preserving memory circuits in normative aging and Alzheimer's Disease	05/01/2021– 04/30/2026 \$1,298,796
Matt Huentelman (Co-I) NIH/NIA/ Banner Health R01AG069453 (Reiman/Caselli/Su/Chen/Langbaum) APOE in the Predisposition to, Protection from and Prevention of Alzheimer's Disease	10/01/2021-03/31/2026 \$675,696
Matt Huentelman (Co-I) NIH/Banner Health P30 AG072980 (Reiman) Arizona Alzheimer's Disease Core Center	09/05/2021 – 06/30/2026 \$84,470
Matt Huentelman (Co-I) NIH/University of Arizona R01HL153112 (Hale) Targeting Resident Cardiac Fibroblast Subpopulations for Protection Against Fibrosis	01/01/2022 – 12/31/2025 \$523,328
Matt Huentelman (Co-I, Lead) NIH/NIA/ Northwestern University U19AG073153 (Rogalski/Geula) Study to uncover pathways to exceptional cognitive resilience in aging (SUPERAGING)	10/01/2021 – 05/31/2026 \$4,127,147

Matt Huentelman (Lead, Co-Lead, Project Lead) NIH/University of Arizona 1U19AG056169-01A1 (Barnes) Precision Aging Network: Closing the Gap Between Cognitive Healthspan and Human Lifespan	09/01/2021 – 08/31/2026 \$18,509,311
Matt Huentelman (PI) TGen Foundation (Huentelman) Gene Surgery	06/01/2020 – 08/31/2022 \$3,846,893
Meredith Hay (PI) NIH/NIA U01AG066623-01 (Hay) IND Enabling Studies for a Novel Mas Receptor Agonist for Treatment of Vascular Dementia	2020-2024 \$5,705,975 Total Project
Meredith Hay (PI) NIH/NIA R43AG069524-01 Formulation of a Novel Therapeutic for Treating Cognitive Impairment in Patients at-risk for Alzheimer's Disease-Related Dementias and Vascular Contributions to Cognitive Impairment	8/15/2021-7/31/2022 \$500,000 Total Project
Michael Malek-Ahmadi (Co-I) NIA/NIA via Mayo Clinic 1RF1AG057547-01 (Kantarci/Gleason) Prevention of Alzheimer's disease in women: risks and benefits of hormone therapy	09/15/2007-06/30/2022 \$751,548 Total Project
Michael Malek-Ahmadi (Co-I) NIH/NIA via ASU P30AG072980 (Reiman) Arizona Alzheimer's Disease Research Center – Data Management & Statistics Core	09/05/2021-06/30/2026 \$1,312,710 Total Project
Michael Malek-Ahmadi (Core Leader; Co-I) NIH/NIA via Dignity Health P01AG014449 (Mufson) Neurobiology of Mild Cognitive Impairment in the Elderly	04/01/2020-03/31/2025 \$793,090 Total Project
Michael Malek-Ahmadi (Project Co-I) State of Arizona DHS via Arizona Alzheimer's Consortium Advanced Imaging and Machine Learning in Alzheimer's Research	07/01/2021-06/30/22 \$250,000
Michael Malek-Ahmadi (Project Co-I) State of Arizona DHS via Arizona Alzheimer's Consortium Statistical and Neuroimaging Data Science Core Resources Serving the Consortium Members	07/01/2021-06/30/22 \$80,000
Michael Sierks (PI) NIH R01AG054048 (Sierks) Protein variants as blood-based biomarkers for diagnosing and staging AD	09/01/2016 - 06/30/2023 \$1,761,841 Total Project

Michael Sierks (PI) NIH via Virtici R43AG076091 (Sierks) A Novel Multiparameter Blood Test for Early Detection of Alzheimer's Disease	01/30/2022 - 08/31/2024 \$26,993 Total Project
Michael Sierks (PI) W81XWH2110837 (Sierks) DOD-ARMY: Army Medical Research Acquisition Activity Targeting Toxic Oligomeric Protein Variants Generated after Traumatic Brain Injury to Decrease Risk of AD	09/01/2021 - 08/31/2024 \$1,295,595 Total Project
Michael Sierks (Project PI) CTR057001 (Coon) Arizona Alzheimer's Consortium (AAC) FY22 AAC FY22: Developing tau therapeutics for treating AD	07/01/2021 - 06/30/2022 \$35,000 Individual Project
Minsub Shim (PI) NIH R15 REAP R15CA246429 Cyclooxygenase-2 Signaling in Cell Senescence and its Role in Chemotherapy-induced Long-term Adverse Sequelae	12/01/2019-11/30/2022 \$450,000 Total Project
Minsub Shim (PI) AZ Dept of Health Services-Arizona Alzheimer's Consortium Geroscience Approach to Alzheimer's Disease: Mitigation of Cellular Senescence by Intermittent Fasting	07/01/2021-06/30/2022 \$21,260 Total Project
Mitra Esfandiarei (PI) NIH R15HL145646 Targeting endothelial function in a genetic mouse model of aortic aneurysm: implications for prevention and therapy	01/15/2019-12/31/2021 \$441,048 Total Project
Nadine Bakkar (Co-PI) Arizona Alzheimer's Consortium (Bakkar/Stokes) Imaging and molecular biomarkers of blood-brain and blood- CSF barrier cerebrovascular health in dementias	07/01/2022-06/30/2023 \$157,500
Nadine Bakkar (PI) Arizona Alzheimer's Consortium Single cell profiling of blood-brain and blood-CSF barriers in dementias	07/01/2021-06/30/2022 \$163,500
Nadine Bakkar (PI) Barrow Neurological Foundation Single nuclear profiling of vascular dysfunction in Amyotrophic lateral sclerosis (ALS)	07/01/2022-06/30/2023 \$110,500
Nafisa Jadavji (PI) 20AIREA35050015 American Heart Association Research Enhancement Award Identification of Developmental Factors Involved in Ischemic Stroke Outcomes in Adulthood and Old Age	01/01/2020-12/31/2021 \$152,735 Total Project

Nafisa Jadavji (PI) AZ Dept of Health Services-Arizona Alzheimer's Consortium Dietary Vitamin B12 Deficiency on Ischemic Stroke Outcome in Aged Female and Male Mice	07/01/2021-06/30/2022 \$8,510 Total Project
Nancy Bae (PI) AZ Dept of Health Services-Arizona Alzheimer's Consortium The Role of Phosphorylation on the Function of the Telomere Protection Protein RAP1	07/01/2021-06/30/2022 \$8,175 Total Project
Nan-kuei Chen NIH R01NS102220 Development of High-Speed and Quantitative Neuro MRI Technologies for Challenging Patient Populations	7/2018-3/2023 \$285,904
Nan-kuei Chen NIH U19AG065169 (Barnes) Precision Aging Network: Closing the Gap Between Cognitive Healthspan and Human Lifespan	09/2021-08/2026 \$300,983 Core D
Nan-kuei Chen NIH/NIA R01AG062543 (Chou) Enhancement of Hippocampal Plasticity Using Repetitive Transcranial Magnetic Stimulation	5/2020-01/2025 \$9,826 Core E
Nan-kuei Chen NIH U01EB029834 (Witte) 4D Transcranial Acoustoelectric Imaging for High Resolution Functional Mapping of Neuronal Currents	9/2020-6/2025 \$9,826 Core E
Nan-kuei Chen NIH R21AG077153 (Chou) Interleaved TMS-fMRI for Hippocampal Stimulation: Modeling Dose-Response Relationship in Amnesic Mild Cognitive Impairment	4/2022-3/2024 \$5,404 Core E
Nan-kuei Chen NIH R01DA045565 (Meade) MRI Data Fusion to Investigate Effects of Drug Abuse on HIV Neurological Complications	3/2018-1/2023 \$15,218 Total Cost
Parichita Choudhury (Project PI) Arizona Alzheimer's Consortium via Arizona DHS Motor Trajectories in neuropathologically-confirmed Lewy Body Disease and other Alzheimer disease and related disorders (ADRD)	07/01/2021 -06/30/2022 \$45,000

Pierre Tariot (Co-I) NIH/NIA R01AG063954 (Langbaum/Bleakley) Establishing the science behind Alzheimer's recruitment registries: opportunities for increasing diversity and accelerating enrollment into trials	09/01/2019-06/30/2024 \$8,793,374 Total Project
Pierre Tariot (PI) NIH/NIA R01AG055444 (Reiman/Tariot/Lopera) Alzheimer's Prevention Initiative ADAD Colombia Trial	04/01/2017-03/31/2023 \$14,893,051 Total Project
Pierre Tariot (PI) NIH/NIA R01AG058468 (Reiman/Aisen/Johnson/Langbaum/Sperling/ Tariot) API / A4 Alzheimer's Prevention Trial	09/01/2018-11/30/2024 \$32,005,950 Total Project
Raffaella Soldi (Research Scientist) 977872 (Sharma) Norman and Sadie Lee Using 'Nano-ghost' Technology to Develop Targeted Treatment of Tumors	01/2020 – 12/2022 \$500,000
Raffaella Soldi (Research Scientist) 3.7000.6510.32400.3001539 (Altin/Sharma) Private Foundation Enhancing the efficacy of tumor-infiltrating lymphocyte (TIL) therapy by enriching tumor neoantigen specificity	04/2021 – 08/2022 \$1,805,518
Raffaella Soldi (Research Scientist) ACOHCOH2720A014 (Sharma) City of Hope National Medical Center Gene Surgery: Small-molecule inhibitor of CDK7	03/2020 – 06/2023 \$845,000
Raffaella Soldi (Research Scientist) ACOHCOH2720A018 (Priceman/Sharma) City of Hope Board of Governor's Multi-targeted CAR-Engineered TILs for Treatment of Advanced Pancreatic Cancer	03/2022 – 02/2024 \$112,500
Ramon Velazquez G09516-3600 Infectious Diseases Society of America (Bertram) The Role of Microbe-induced Necroptotic Death in Tauopathy	01/2021-01/2022 \$100,000
Ramon Velazquez NIH/NIA P30AG01960 (Reiman) Arizona Alzheimer's Disease Core Center	08/2016-06/2022 \$13,001,888
Ramon Velazquez The Edson Initiative for Dementia Care and Solutions Endowment via ASU Glyphosate Exposure as a Risk Factor for Cognitive Aging and Alzheimer's Disease	12/2020-02/2022 \$64,035

Ramon Velazquez NIH/NIA P30AG072980 (Reiman) Arizona Alzheimer's Disease Research Center	09/2021-06/2026 \$15,727,544
Ramon Velazquez (PI) NIH R01AG062500 S6K1 as a novel link between aging and Alzheimer's disease	04/2019-02/2024 \$3,040,398
Ramon Velazquez (PI) NIH R01AG059627 Identify common mechanisms of neurodegeneration between Alzheimer's disease and Down syndrome	09/2018-05/2023 \$3,112,707
Raymond Migrino and Jonathan Lifshitz (dual PIs) U.S. Dept. of Veterans Affairs VA Merit I01002691 Mechanistic role of vascular dysfunction in TBI-mediated cognitive dysfunction	04/01/2021 – 03/31/2025 \$1,200,000 Total Project
Richard Caselli NIH via ASU R01AG054048 (Sierks) Protein Variants as Blood-based Biomarkers for Diagnosing and Staging AD	09/2016-06/2022 \$168,429
Richard Caselli NIH/NINDS via ASU R21AG065942 (Wang) Developing a Univariate Neurodegeneration Imaging Biomarker with Optimal Transportation	08/2020-07/2022 \$23,081
Richard Caselli SPARK Neuro Development of an EEG Diagnostic for Alzheimer's Disease: A Feasibility Study	06/2021-05/2022 \$70,785
Richard Caselli (Associate Director) NIH/NIA P30AG072980 (Reiman) Core A: ADCC Admin Core: Alzheimer's Disease Core Center	09/01/21-06/30/26 \$18,962
Richard Caselli (PI) NIH/NIA R01AG069453 (Reiman/Caselli) APOE in the Predisposition To, Protection From, and Prevention of Alzheimer's Disease	07/01/20-6/30/25 \$126,358
Richard Caselli (PI) ADHS14-052688 Arizona Department of Health Services Normal and Pathological Aging (Preclinical Alzheimer's Disease)	07/01/21-06/30/23 \$700,000
Richard Caselli (PI) P01 (Reiman/Caselli) Alzheimer's Disease Research Center	07/01/21-06/30/26

Richard Caselli (PI) ASU Collaborative Fund Investigating African American-specific AD-related ABCA7 variants using isogenic hiPSCs	07/2021 – 06/2022 \$80,000
Richard Caselli (PI/Core Leader) NIH/NIA via Banner Health P30AG072980 (Reiman) Arizona Alzheimer's Disease Research Center Core B: ADCC Clinical Core	09/01/21-06/30/26 \$191,728
Richard Caselli (Statistical Support) NIH/NIA via Banner Health P30AG072980 (Reiman) Core C: ADCC Data Core: Alzheimer's Disease Research Center	09/01/21-06/30/26 \$18,962
Robert Alexander Eli Lilly and Company TRAILBLAZER-ALZ3	07/2021-06/2027 \$4,116,286
Robert Alexander (Co-I) NIH/NIA R01AG055444 (Reiman/Tariot/Lopera) Alzheimer's Prevention Initiative ADAD Colombia Trial	04/2017-03/2023 \$14,893,051
Robert Alexander (Co-I) NIH/NIA R01AG058468 (Reiman) API / A4 Alzheimer's Prevention Trial	09/2018-11/2024 \$32,005,950
Robert Alexander (Co-I) NIH/NIA via IMM Safety/Tolerability/Immunogenicity of first-in-human A β DNA vaccine, AV-1959D Phase 1 trials in early-stage AD subjects: based on IND18953 cleared by FDA	08/2022-11/2027 \$95,630
Robert Alexander (Project PI) Arizona Alzheimer's Consortium via Arizona DHS Clinicopathological Correlates of Rapidly Progressive Alzheimer's Disease	07/01/2021 – 06/30/2022 \$30,000
Roberta Brinton (Co-I) NIH/NIA U01AG063768 (Rodgers) IND Enabling Studies for RASRx 1902, a novel Mas receptor agonist, for treatment of cognitive impairment in patients at risk for Alzheimer's disease	05/01/2020-04/30/2024 \$6,108,279
Roberta Brinton (Co-I) NIH/NIA U19AG065169 (Barnes) Precision Aging Network: Closing the Gap Between Cognitive Healthspan and Human Lifespan	09/01/2021-08/31/2026 \$59,988,951

Roberta Brinton (Co-I) NIH via Duke University RF1AG059093 (Kaddurah-Daouk) Metabolic Networks and Pathways Predictive of Sex Differences in AD Risk and Responsiveness to Treatment	08/01/2018-03/31/2022 \$640,519
Roberta Brinton (Core Co-Leader) NIH/NIA via Banner Health P30AG072980 (Reiman) Arizona Alzheimer's Disease Research Center	09/05/2021-06/30/2026 \$625,500
Roberta Brinton (PI) NIH/NIA R01AG075122 (Brinton) PhytoSERM Efficacy to Prevent Menopause Associated Decline in Brain Metabolism and Cognition: A Double-Blind, Randomized, Placebo-Controlled Phase 2 Clinical Trial	12/01/2021-11/30/2026 \$7,735,907
Roberta Brinton (PI) NIH/NINDS R25NS107185 (Brinton/Rodgers/Boyd) Undergraduate Readyng for Burgeoning Research for American Indian Neuroscientists	07/01/2019-06/30/2024 \$1,477,249
Roberta Brinton (PI) NIH/NIA R01AG057931 (Brinton) Sex Differences in the Molecular Determinants of Alzheimer's Disease Risk: Prodromal Endophenotype	09/01/2018-05/31/2023 \$5,706,378
Roberta Brinton (PI) NIH/NIA R01AG063826 (Brinton) Allopregnanalone as Regenerative Therapeutic for Alzheimer's: Phase 2 Clinical Trial	08/15/2019-04/30/2025 \$37,329,334
Roberta Brinton (PI) Alzheimer's Association 18PTC-R-590498 Advancing Allopregnanalone as a Regenerative Therapeutic for Alzheimer's	04/01/2019-03/31/2023 \$1,000,000
Roberta Brinton (PI) NIH/NIA P01AG026572 (Brinton) Perimenopause in Brain Aging and Alzheimer's Disease	09/01/2021 – 08/31/2026 \$15,168,816
Sarah Stabenfeldt (Co-I) John Templeton Foundation 62189 (Bennett) Craftwork as Soulwork: Sanctifying Scientific Practice among Genetics Researchers	07/01/2021-06/30/2023 \$234,437
Sarah Stabenfeldt (PI) NIH/NINDS R01NS116657 (Stabenfeldt/Sirianni) Exploiting sex-dependent brain injury response for nanoparticle therapeutics	01/01/2021-11/30/2025 \$2,551,485

Sarah Stabenfeldt (PI) NIH/NINDS R03NS122018 (Stabenfeldt/Bowser) Linking TBI secondary injuries to FTLD- and ALS-like neurodegeneration	08/15/2021-07/31/2023 \$100,000
Stephen Cowen (Co-I) NIH/NIDA P30DA051355 The Center of Excellence in Addiction Studies (CEAS)	08/2021 – 05/2026 \$6,676,282 Total Cost
Stephen Cowen (Co-I) NIH R01NS123424 Control of the time course of dopamine release through optimized electrical brain stimulation	06/21/2021 - 05/31/2026 \$1,833,908 Total Cost
Stephen Cowen (Co-I) NIH/NINDS NS122805-01 (Falk) Mechanisms of Low-Dose Ketamine Treatment for Parkinson's Disease	07/2021– 06/2025 \$ 1,495,839 Total Cost
Stephen Cowen (Co-I) NIH/NBIB U01EB029834 (Witte) 4D Transcranial Acoustoelectric Imaging for High Resolution Functional Mapping of Neuronal Currents	09/2020 – 06/2025 \$ 3,414,477 Total Cost
Stephen Cowen (Co-I) NIH R21NS123512 (Miller) Alpha-synuclein driven cellular changes and vocal dysfunction in Parkinson's Disease	07/2021 - 12/2022 \$ 415,482 Total Cost
Steven Rapcsak (Site PI) NIH/NIA via ASU P30AG072980 (Reiman) Arizona Alzheimer's Disease Research Center	09/2021-06/2026 \$911,967
Sunil Sharma (PI) DOD W81XWH1810617 (Sharma & Welm) RON kinase as a multi-faceted therapeutic target for metastatic breast cancer	09/2018 – 09/2023 \$3,386,423
Sunil Sharma (PI) Norman and Sadie Lee 977872 (Sharma) Using 'Nano-ghost' Technology to Develop Targeted Treatment of Tumors	01/2020 – 12/2022 \$500,000
Sunil Sharma (PI) 3.7000.6510.32400.3001539 (Altin & Sharma) Private Foundation Enhancing the efficacy of tumor-infiltrating lymphocyte (TIL) therapy by enriching tumor neoantigen specificity	04/2021 – 08/2022 \$1,805,518

Sunil Sharma (PI) ACOHCOH2720A014 (Sharma) City of Hope National Medical Center Gene Surgery: Small-molecule inhibitor of CDK7	03/2020 – 06/2023 \$845,000
Sunil Sharma (PI) ATFDG012440A008 (Trent) Discount Tire TGen/Discount Tire Wellness Trial	10/2019 – 09/30/2022 \$603,865
Sunil Sharma (PI) ACOHCOH2720A018 (Sunil Sharma (PI) Priceman & Sharma) City of Hope Board of Governor's Multi-targeted CAR-Engineered TILs for Treatment of Advanced Pancreatic Cancer	03/2022 – 02/2024 \$112,500
Sunil Sharma (PI) ATFDG012720A006 (Sharma) AZ Blue Cross Blue Shield Charitable Grant from Arizona Blue Cross Blue Shield	10/2021 – 09/2022 \$20,000
Tamara Turner (PI) AZ Dept of Health Services-Arizona Alzheimer's Consortium Music and Dementia: A Manualized Intervention Incorporating Music in Occupational Therapy for Persons Living with Dementia	07/01/2021-06/30/2022 \$471,912 Total Project
Theodore Trouard (Site Co-I) NIH R41NS124450 (Morrison) NanO2 as a Cerebroprotectant in a tMCAO Stroke Model in Mice	9/15/2021-8/31/2022 \$478,050 Total Cost
Theodore Trouard (Site PI) NIH R43AG067894 Targeted ultrasound contrast agents for the disruption of Alzheimer's plaques	8/1/2020-4/30/2023 \$395,506 Total Cost
Thomas Beach NIH via UCSF Gladstone P01AG073082 (Mucke) Decoding the Multifactorial Etiology of Neural Network Dysfunction in Alzheimer's Disease	08/15/21-7/30/26 \$200,575 Total Project
Thomas Beach NIH via UCSD R01AG074221 (Sundermann) Sex Differences in the Clinical Expression of Alzheimer's Disease Neuropathology and Their Underlying Biological Mechanisms	08/15/2021-4/2026 \$128,786 Total Project

Thomas Beach NIH via Binghamton University R01NS122226 (Bishop) Interrogating maladaptive serotonin raphe-striatal plasticity in L-DOPA-induced dyskinesia	12/2021-11/2026 \$54,597 Total Project
Thomas Beach NIH via University of Arizona R03AG071903 (Hutchinson) Microstructural MRI microscopy of post-mortem specimens to identify and improve markers of Alzheimer's Disease pathology	06/2021-5/2023 \$31,907 Total Project
Thomas Beach ABRC via Mayo Clinic Arizona CTR056041 Submandibular gland needle core biopsy as a tissue biomarker the diagnosis of Parkinson's disease and the monitoring of disease progression	07/01/2021-6/30/2024 \$182,963 Total Project
Thomas Beach NIH via Stanford University R01AI162850 (Mizgerd) Pulmonary Pathophysiology Sub-Phenotypes of Pneumonia	04/2022-03/2027 \$203,196 Total Project
Thomas Beach NIH via Florida International University 1R21AG072561-01 (Gu) Targeting Whole-body Fatty Acid Metabolism in Alzheimer's Disease, with Special Interest in Lauric acid	06/2021-05/2023 \$40,483 Total Project
Thomas Beach NIH via Case Western University R01AG067607 (Kraus) Skin biomarkers for diagnosing and characterizing AD and ADRD	09/2021-06/2026 \$27,714 Total Project
Thomas Beach (PI) NIH/NINDS R01NS118669 (Beach) Blinded Comparison of Different Alpha-Synuclein Seeding Assays as Cutaneous Biomarkers of Lewy Body Dementias	07/01/2021– 06/30/2025 \$3,195,450 Total Project
Thomas Beach (Co-I) NIH via University of CA-Irvine RF1AG029479 (Mukherjee) PET Imaging Agents for a4b2 Nicotinic Receptors	08/15/2019-07/31/2022 \$123,104 Total Project
Thomas Beach (Co-I) NIH via Ohio State University R56AG066782 (Fu) The role of ectodermal-neural cortex 1 in selective vulnerability in aging and Alzheimer's disease	09/17/2020-08/31/2021 \$43,544 Total Project
Thomas Beach (Co-I) NIH via UAB R56NS117465 (Volpicelli-Daley) Alpha-synuclein aggregate induced synapse loss is a pathological event contributing to Lewy body dementias	09/01/2020-08/31/2021 \$43,171 Total Project

Thomas Beach (Co-I) NIH via UCSB R01AG062479 (Kosik) The complex interaction between Alzheimer's drivers and aging	09/15/2020-08/31/2024 \$382,349 Total Project
Thomas Beach (Co-I) MJFF via BWH ASAP-000301(Scherzer) Parkinson5D: deconstructing proximal disease mechanisms across cells, space, and progression	10/01/2020-09/30/2023 \$119,531 Total Project
Thomas Beach (Co-I) NIH via University of Kentucky R01AG068331 (Ebbert) Using long-range technologies as a multi-omic approach to understand Alzheimer's disease in brain tissue	06/01/2021-05/31/2025 \$201,471 Total Project
Thomas Beach (Co-I) 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	08/01/2017 – 12/31/2022 \$395,695 Total Project
Thomas Beach (Co-I) NIH/NIA via ASU 1P30AG072980-01 (Reiman) Arizona Alzheimer's Disease Research Center – Biomarker Core	07/01/2021-06/30/2026 \$4,984,211 Total Project
Thomas Beach (Co-I) NIH/NIA via University of Wisconsin-Madison R01AG070883 (Kind) The Neighborhoods Study: Contextual Disadvantage and Alzheimer's Disease and Related Dementias	03/2021-02/2026 \$264,852 Total Project
Thomas Beach (Consultant) NIH via Boston University R33HL137081 (Kepler) The B cell repertoire as a window into the nature and impact of the lung virome	10/08/2019-04/30/2022 \$59,068 Total Project
Thomas Beach (Consultant) Phoenix VA Health Care System 2I01BX003767-05 (Migrino) Discovering novel mechanisms for aging-related dementia: probing medin and abeta vasculopathy	05/17/2021-05/16/2023 \$30,000 Total Project
Thomas Beach (Co-PI) Gates Ventures via Banner Alzheimer's Foundation Resources for the Diagnostic and Prognostic Validation of Blood-Based Biomarkers of Alzheimer's Disease, Parkinson's Disease and Related Disorders	09/01/2020-08/31/2024 \$3,085,720 Total Project

Thomas Beach (Core Leader) NIH/NIA via ASU P30AG019610 (Reiman) Arizona Alzheimer's Disease Research Center – Neuropathology Core	07/01/2016-06/30/2023 \$1,261,052 Total Project
Thomas Beach (Core Leader) NIH/NIA via ASU P30AG072980 (Reiman) Arizona Alzheimer's Disease Research Center – Neuropathology Core	09/05/2021-06/30/2026 \$1,636,000 Total Project
Thomas Beach (PI) MJFF-020674 (Beach) Systemic Synuclein Sampling Study	06/23/2016-04/01/2023 \$532,948 Total Project
Thomas Beach (PI, Neuropathology Core) NIH/NIA via ASU 3P30AG019610-20S1 (Reiman) Arizona Alzheimer's Disease Research Center - Presence and Neuropathological Consequences of CNS Covid-19 in Consecutive Autopsies During the Worldwide Pandemic	07/01/2020-06/30/2023 \$386,476 Total Project
Tom Broderick (PI) Phoenix VA Healthcare System Mechanistic Role of Vascular Dysfunction in TBI-mediated Cognitive Dysfunction	04/15/2021-04/14/2023 \$28,760 Total Project
Yalin Wang (Co-I) National Science Foundation (NSF) 2126303 (Jennewein) CC* Compute: The Arizona Federated Open Research Computing Enclave (AFORCE), an Artificial Intelligence and Bioinformatics Innovation: An Integrative Collaborative Center for Nutrition for Precision Health	9/1/2021-8/31/2023 \$396,874
Yalin Wang (Co-I) NIH F31MH122107 (Walsh) Are aging outcomes worse for women with autism? Sex differences in the neurocircuitry of symptom camouflaging and its vulnerability to aging	9/15/2021-9/14/2023 \$115,567
Yalin Wang (MPI) NIH R01EY032125 (Wang/Lu) Hierarchical Bayesian Analysis of Retinotopic Maps of the Human Visual Cortex with Conformal Geometry	7/1/2021-6/30/2025 \$1,559,565
Yalin Wang (PI) Children's Hospital Los Angeles R01DE030286 (Lepore) Early Joint Cranial and Brain Development from Fetal and Pediatric Imaging	9/15/2021 – 5/31/2026 \$230,192

Yalin Wang (PI) NIH R21AG065942 (Wang) Developing a Univariate Neurodegeneration Imaging Biomarker with Optimal Transport	8/1/2020-7/31/2023 \$444,976
Yalin Wang (PI) Children's Hospital Los Angeles R01EB025032 (Lepore) Predicting the Early Childhood Outcomes of Preterm Brain Shape Abnormalities	9/21/2017-6/30/2023 \$497,482
Yalin Wang (PI) Children's Hospital Los Angeles R01EB025032-04S1 (Lepore) Influence of APOE4 Genotype on Neonatal Cortical Morphology	9/22/2020 – 6/30/2023 \$156,995
Yalin Wang (PI) Mayo Clinic (Wang) Pipeline for Image-Genomic Data Integrative Analysis	1/1/2020–12/21/2022 \$89,000
Yi Su (Co-I) NIH/NIA P30AG019610 (Reiman) Arizona Alzheimer's Disease Core Center – Brain Imaging & Fluid Biomarker Core	07/01/2018-06/30/2023 \$8,948,605 Total Project
Yi Su (Co-I) NIH/NIA R01AG055444 (Reiman/Tariot/Lopera) Alzheimer's Prevention Initiative ADAD Colombia Trial	04/15/2018-03/31/2023 \$14,893,051 Total Project
Yi Su (Co-I) NIH/NIA R01AG058468 (Reiman/Aisen/Johnson/Langbaum/Sperling/ Tariot) API / A4 Alzheimer's Prevention Trial	09/01/2018-11/30/2024 \$32,005,950 Total Project
Yi Su (Co-I) U54 MD000507 (Manson/Buchwald) NIH/NIMHH via University of Colorado Denver American Indian and Alaska Native Health Disparities	05/01/2019-04/30/2022 \$178,067 Total Project
Yi Su (Co-I) U19 AG024904 (Weiner) NIH/NIA via Northern California Institute Res & Educ. Alzheimer's Disease Neuroimaging Initiative	09/30/2017-7/31/2022 \$400,000 Total Project
Yi Su (Co-I) NIH via MS Technologies R42AG053149 (Lure) Multi-Modality Image Data Fusion and Machine Learning Approaches for Personalized Diagnostics and Prognostics of MCI due to AD	01/01/2021-12/31/2022 \$241,309 Total Project

Yi Su (Co-I) NIH/NIA via ASU R21AG065942 (Wang) Developing a Univariate Neurodegeneration Imaging Biomarker with Optimal Transportation	08/01/2020-07/31/2022 \$17,230 Total Project
Yi Su (Co-I) NIH/NIA via Boston University U01NS093334 (Stern) Chronic Traumatic Encephalopathy: Detection, Diagnosis, Course, and Risk Factors	12/01/2020-11/30/2022 \$112,381 Total Project
Yi Su (Co-I) NIH/NIA via T3D Therapeutics R01AG061122 (Didsbury) Phase 2 Randomized, Double-Blind, Placebo-Controlled Clinical Trial of T3D-959 in Mild to Moderate Alzheimer's Disease Subjects	03/01/2021-02/28/2022 \$14,256 Total Project
Yi Su (Core Co-Leader) NIH/NIA via ASU P30AG072980 (Reiman) Arizona Alzheimer's Disease Research Center – Data Management & Statistics Core	09/01/2021-06/30/2026 \$1,312,710 Total Project
Yi Su (Core Co-Leader) NIH/NIA via ASU P30AG072980 (Reiman) Arizona Alzheimer's Disease Research Center – Biomarker Core	07/01/2021-06/30/2026 \$4,984,211 Total Project
Yi Su (PI) NIH/NIA R01AG069453 (Reiman) APOE in the Predisposition to, Protection from and Prevention of Alzheimer's Disease	09/30/2020-03/31/2026 \$27,473,070 Total Project
Yi Su (PI) Alzheimer's Association AARG17532945 (Su) Amyloid PET as a biomarker for white matter integrity in Alzheimer disease	10/01/2017-9/30/2021 \$150,000 Total Project
Yi Su (PI) NIH/NIA RF1AG073424 (Su) Tracer harmonization for amyloid and tau PET imaging using statistical and deep learning techniques	08/01/2022-07/31/2025 \$2,282,378 Total Project
Yi Su (Project PI) State of Arizona via Arizona Alzheimer's Research Consortium Advanced Imaging and Machine Learning in Alzheimer's Research	07/01/2021-06/30/2022 \$250,000
Yi Su (Project PI) State of Arizona via Arizona Alzheimer's Research Consortium Statistical and Neuroimaging Data Science Core Resources Serving the Consortium Members	07/01/2021-06/30/2022 \$80,000

Yin, Fei Yin (Project Leader) NIH/NIA P01AG026572 (Brinton) Perimenopause in Brain Aging and Alzheimer's Disease Project 1: Metabolic Mechanisms of Perimenopausal Neuroimmune Transformation: Therapeutic Targets and Windows	04/01/2021-05/31/2026 \$15,168,816 Total \$1,712,931 Project 1
Ying-hui Chou (Co-I) NIH/NIA R01 AG061888-02 (Wilson) Evaluating the Neurocomputational Mechanisms of Explore- Exploit Decision Making in Older Adults Neuroimaging and TMS studies of explore-exploit decision making in older adults	1/15/2020-1/14/2024 \$1,150,000 Total Project
Ying-hui Chou (Co-I) NIH/NBIB R01 EB028662 (Witte) 4D Transcranial acoustoelectric imaging for high resolution functional mapping of neuronal currents	9/2020-6/2025 \$3,434,477 Total Project
Ying-hui Chou (Co-I) DOD PR192753 (Killgore) DOD, Medical Research Program Discovery Award Transcranial Magnetic Stimulation of the Default Mode Network to Improve Sleep	10/2020-9/2022 \$306,995 Total Project
Ying-hui Chou (PI) NIH/NIA R01 AG062543-01A1 (Chou) Enhancement of hippocampal plasticity using repetitive transcranial magnetic stimulation	5/1/2020-1/31/2025 \$3,629,382 Total Cost
Ying-hui Chou (PI) NIH/NIA R21 AG077153 (Chou) Interleaved TBS-fMRI for Spaced Hippocampal Stimulation: Modeling Dose-Response Relationship in Amnesic Mild Cognitive Impairment	04/01/2022 – 03/31/2024 \$409,171 Total Project
Yonas Geda (Co-I) NIH/NIA R01AG057708 APOE in the Predisposition to, Protection from and Prevention of Alzheimer 's disease	11/2020 – 03/2026 \$111,475
Yonas Geda (PI) NIH/NIA R01AG057708 (Geda) Pathways linking neuropsychiatric symptoms with Alzheimer's disease neuroimaging biomarkers and the outcome of incident Mild Cognitive Impairment/Dementia.	05/01/2018 – 11/30/2022 \$356,362
Yonas Geda (PI) NIH/NIA 5U01AG006786-34 (MCR to Dr. Geda) Alzheimer's Disease Patient Registry Renewal	07/2019 - 06/2024 \$22,950 for 07/2021 – 06/2022

Yonas Geda (PI)
NIH/NIA P30AG019610 (Federal sub award)
Alzheimer's Disease Core Center

07/2016 – 12/2021

Pending Grants

Ali Bilgin (Co-I) NIH (Altbach/Deshpande/Wu) Quantitative MRI and Deep Learning Technologies for Classification of NAFLD	04/01/2022-03/31/2027 \$1,344,284 Total Project
Ali Bilgin (Co-I) National Institutes of Health (Saranathan) Next-Generation Thalamic Nuclei Visualization and Segmentation Methods	07/01/2022-06/30/2026 \$2,191,177 Total Project
Ali Bilgin (Co-I) National Science Foundation (Enikov) IGE: Internship-Based Master of Engineering in Intelligent Systems	10/01/2022-09/30/2025 \$496,802 Total Project
Ali Bilgin (PI) Global Engineering Research and Technologies/United States Department of Defense Data-Driven Physics-Based Modeling Tools to Determine Effective Mechanical Properties of As-Built Composite Structures	6/01/2022-05/31/2023 \$26,124 Total Project
David Brafman (PI) Department of Defense 2021-01T-T026 (PI: Brafman) Development of Low-Cost, Paper-Based System for the Detection of Adventitious Agents in Biomanufacturing Processes	07/01/2022-06/30/2024
David Brafman (PI) 1 S10 OD032287-01 BD FACSymphony S6 cell sorter	07/01/2022-06/30/2023
David Brafman (PI) 1 R21 AG079279-01 Establishing Genotype-to-Phenotype Relationships Between Alzheimer's Related BIN1 Variants	07/01/2022-06/30/2024
David Brafman (PI) 1 R01 AG079332-01 Investigating the protective mechanisms of APOE2	09/01/2022-08/31/2027
David Brafman (PI) 1 R01 AG080725-01 Dissecting the mechanisms by which endosomal-associated risk genes modulate Alzheimer's disease-related phenotypes	09/01/2022-08/31/2027
David Brafman (PI) 1 R21 1AG080384-01 Determining the Interactions between APOE and CLU Risk Variants	09/01/2022-08/31/2024

David Brafman (PI) 1 R21 AG080301-01 Determining the impact of RAB10 on Alzheimer's disease-related phenotype	09/01/2022-08/31/2024
David W. Coon (Co-I) NIH FP00028895_Res1 (Yu) 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	1/2/2023-1/1/2028 \$641,477
David W. Coon (Co-I) NIH FP00030876 (Byrd) The Epidemiology of Cognitive Decline in African Americans: Identifying Risk and Protective Factors	7/1/2022-6/30/2027 \$115,462
David W. Coon (Co-I) National Endowment for the Arts (NEA) FP00032441 (Underiner) The Epidemiology of Cognitive Decline in African Americans: Identifying Risk and Protective Factors	7/1/2022-6/30/2024 \$68,434
David W. Coon (Co-I) FP00032638 (Ng) Arizona State University Foundation (ASUF) / National Academy of Medicine (NAM) Bio-psycho-social Effects of a Tailored Mindfulness Intervention in Preclinical Dementia: A Randomized Controlled Trial	9/1/2022-8/31/2023 \$45,455
David W. Coon (PI) FP00032867 (Coon) University of Arizona / HHS: National Institutes of Health (NIH) Daily stressors and health among Hispanic and non-Hispanic White dementia caregivers: the role of emotion regulation and culture	12/1/2022-11/30/2024 \$5,442
David W. Coon (PI) FP33635 (Coon) Arizona Alzheimer's Consortium / Arizona Department of Health Services (ADHS) Arizona Alzheimer's Consortium (AAC) FY23 - Match Projects	7/1/2022-6/30/2023 \$350,000
David W. Coon (PI) FP33635 (Coon) Arizona Alzheimer's Consortium / Arizona Department of Health Services (ADHS) Arizona Alzheimer's Consortium (AAC) FY23 – Non-Match Projects	7/1/2022-6/30/2023 \$200,000

David W. Coon (PI) NIH FP00032707 (Yu) Effects of Combined Aerobic and Resistance Exercise on Sleep, Cognition, and Blood Biomarkers as Surrogate Endpoints for Cognition in Older Adults with Amnesic Mild Cognitive Impairment (aka The CARE Trial)	7/1/2023 – 6/30/2028 \$3,906,203
Diego Mastroeni Infectious Disease Society of America Brain Gut-Axis	\$100,000
Diego Mastroeni (Co-PI) FY20 PRARP CSRA, Department of Defense Precision targeting of the rod microglia variant in neurological injury and disease	\$190,000
Diego Mastroeni (Co-PI) NIH R01 Novel tools to probe the rod microglia variant in neurological disease.	\$873,000
Diego Mastroeni (Co-PI) NIH R01 Novel Nanobodies Target Earliest Forms of Pathogenic Amyloid and TDP-43 in Neuronal and Microglial Cells	\$2,400,000
Diego Mastroeni (Co-PI) NIH R21 Human methylated DNA and metabolites in wastewater: Population biomarkers for susceptibility to neurodegenerative diseases	\$450,000
Diego Mastroeni (PI) The Alzheimer's Association Rapid Program in Dementia	\$50,000
Diego Mastroeni (PI) NIH R01 MAC activation and Alzheimer's Synapse	\$800,000
Diego Mastroeni (PI) NIH R01 Membrane Attack Complex and Vascular Contributions to Dementia.	\$2,500,000
Diego Mastroeni (PI) NIH R01 The Effect of ApoE-E4 Homozygosity on Human Microglial Clearance	\$2,800,000
Diego Mastroeni (PI) NIH R21 Using Peripheral Microglial Exosomes to predict brain inflammation in the human Parkinson's brain	\$497,000

Elizabeth Hutchinson (Co-PI) CDMRP/DoD BAA (Juliano) A Military-Relevant Brain Injury Model in a Gyrencephalic Animal with Therapeutic Investigation	Rolling, duration 3-years \$85,276 Total Project
Elizabeth Hutchinson (Co-PI) Novartis W81XWH-22-S-CRRP (Lifshitz) Reeling in rods: Packing a tackle box to lure the rod microglia isoform that catches inflamed CNS tissue	04/01/2023-03/31/2025 \$1M Total Project
Elizabeth Hutchinson (MPI) NIH/NIA via UCSD R01943783 (Frank/Hutchinson/Bondi) Joint Estimation Diffusion Imaging (JEDI) for Improved Tissue Characterization and Neural Connectivity in Aging and Alzheimer's Disease	04/01/2023-03/31/2028 \$2,022,918 Total Subaward
Elizabeth Hutchinson (PI) CDMRP/DoD W81XWH-22-S-CRRP (Hutchinson) Transcranial Ultrasound Treatment (tUSx) as a Point-of-Injury Intervention Following Brain Trauma	09/30/2023-09/30/2025 \$2.2M Total Project
Emily Cope (PI) Pending-year 5 (Cope) Arizona Alzheimer's Consortium Alzheimer's /AZDHS Arizona Statewide Alzheimer's Research	07/01/2022-06/30/2023 \$150,000 Total Project
Emily Cope (Project Lead) Pending (Baldwin) NIH/ NIMHD Southwest Health Equity Research Collaborative (SHERC) <i>Renewal</i>	09/2022 – 08/2027 \$27,669,552 Total Project
Eric Reiman (Co-I) NIH/NIA via MGH (Quiroz) Relationship between tau pathology and cognitive impairment in autosomal dominant Alzheimer's disease	04/2023-03/2024 \$208,812
Fei Yin (PI) NIH/NIA R01 AG081317 (Yin) Disrupted Lipid Catabolism in Alzheimer's Disease	04/01/2023-03/31/2028 \$2,794,798 Total Project
Geidy Serrano DOD CDMRP via ASU (Sierks) A Novel Multiparameter Blood Test for Early Detection of Frontotemporal Dementia	05/2023-04/2027 \$139,288
Geidy Serrano (Co-PI) NIH (Beach/Serrano) Neuropathological Consequences and Viral Brain Persistence after SARS-CoV-2 Infection in Consecutive Autopsies from a Longitudinal Clinicopathological Study of Aging and Neurodegenerative Disorders	04/01/2023-03/31/2028 \$6,277,699

Gene E. Alexander (Co-I) NIH/NIA R01AG068098 (Andrews-Hanna, Grilli) Tracking autobiographical thoughts: a smartphone-based approach to identifying cognitive correlates of Alzheimer's disease biomarkers and risk factors in clinically normal older adults	7/01/22-6/30/27 \$4,600,829 Total Cost
Greg Caporaso (Co-I) RFA-HD-23-006 (Herbst-Kralovetz) NIH via University of Arizona Integrating Multi-Omics and 3D Models to Develop Non-Invasive Diagnostics for Adenomyosis.	12/01/2022-11/30/2027 \$332,286 Total Subcontract
Greg Caporaso (Co-I) PAR-19-198 (Herbst-Kralovetz) NIH via University of Arizona Microbiome-Mediated Immune Mechanisms that Affect the Efficacy of Endometrial Cancer	07/01/2020-06/30/2025 \$455,040 Total Subcontract
Greg Caporaso (Co-I) PAR-18-654 (Herbst-Kralovetz) NIH via University of Arizona Longitudinal multi-omics analysis and elucidation of the functional impact of the cervicovaginal microenvironment in Hispanic women to reduce cervical cancer disparities	04/01/2020-03/31/2025 \$455,040
Greg Caporaso (PI) CZI-EOSS5 Chan-Zuckerberg Initiative / Silicon Valley Community Foundation Improving QIIME 2 pathogen identification and developer community tools	11/01/2022 - 10/31/2024 \$400,000
Heather Bimonte-Nelson (Co-I) FP00032590 (Gipson-Reichardt) NIH via University of Kentucky Nicotine Reward Circuitry: Impact of Ovarian Hormones and Contraceptive Estrogen	09/01/2022-08/30/2027 \$171,878 Total Project
Heather Bimonte-Nelson (Co-I) FP00032850 (Gipson-Reichardt) NIH via University of Kentucky Contributions of Progestins Independently and Interactively with Contraceptive Estrogen to Nicotine Use	09/01/2022-08/30/2024 \$34,038 Total Project
Heather Bimonte-Nelson (Co-I) FP33635 (Coon) Arizona Alzheimer's Consortium, Arizona Dep of Health Services A Preclinical Evaluation of the Impact of Estrogen Therapy after Variations in Surgical Menopause: Effects on Cognition, Anxiety, and Inflammatory Markers	07/01/2022-06/30/2023 \$350,000 Total Project

Jeremy Pruzin (Co-I) NIH via ASU (Yu) Effects of Combined Aerobic and Resistance Exercise on Sleep, Cognition, and Blood Biomarkers as Surrogate Endpoints for Cognition in Older Adults with Amnesic Mild Cognitive Impairment (AKA: The CARE Trial)	07/01/2023-06/30/2028 \$408,128
Jonathan Lifshitz (PI) U.S. Dept. of Veterans Affairs IK6 RX003678 RR&D Research Career Scientist Award Application	11/01/2020 – 10/31/2025 \$798,361 Total Project
Jonathan Lifshitz (PI) NIH/NICHD R01 HD110860 Gravida traumatic brain injury (TBI) impacts neurobehavioral and neurocircuitry phenotypes of the offspring	09/01/2022 – 08/31/2025 \$1,818,842 Total Project
Jonathan Lifshitz (PI) U.S. Dept. of Veterans Affairs VA Merit I01 BX005956 Analytical Modeling of Acquired Neurological Injury with Rich Experimental Data Sets	04/01/2022 – 03/31/2026 \$1,200,000 Total Project
Jonathan Lifshitz (PI) U.S. Dept. of Veterans Affairs VA Merit I01 RX004536 Psychoplastogens to make the injured brain receptive to cognitive rehabilitation during the chronic period of TBI	10/1/2022 – 09/30/2026 \$1,200,000 Total Project
Jonathan Lifshitz (PI) NIH/NINDS R21 NS131877 Miniscope in vivo imaging of cumulative traumatic brain injury	4/01/2023 – 3/31/2025 \$422,125 Total Project
Jonathan Lifshitz and Sarah Stabenfeldt (dual PI) NIH/NIA R01 AG077768 Molecular Tool Development to Identify, Isolate, and Interrogate the Rod Microglia Phenotype in Neurological Disease and Injury	09/01/2022 – 08/31/2026 \$2,951,028 Total Project
Judith Su (Co-PI) NSF MRI: Acquisition of Near-Ambient Pressure X-ray Photoelectron Spectroscopy with In-Situ Electrochemical Cell for Materials Research	08/01/2022-07/31/2025 \$999,600 Total Project
Judith Su (PI) Chan-Zuckerberg Initiative Chan-Zuckerberg Initiative – Science Diversity Leadership	09/01/2022-08/31/2027 \$1150,000 Total Project
Kendall Van Keuren-Jensen (Co-I) NIH/ University of California, San Diego (UCSD) UH3CA241687 (Laurent) HuBMAP Administrative Supplement 1	04/2023 – 03/2024 \$28,800

Kendall Van Keuren-Jensen (Co-I) NIH/ Barrow Neurological Institute, SJHMC R01 (Mufson & Perez) Default Mode Network dysfunction in Down Syndrome	04/2023 – 03/2028 \$676,647
Kendall Van Keuren-Jensen (Co-I) NIH/UCSF R01 (Finkbeiner) Integrative Imaging and Multi-omic Analysis of Spatial Transcriptomics	04/2023 – 03/2028 \$720,000
Kendall Van Keuren-Jensen (Co-I) Arizona Alzheimer's Consortium –Az Health Dept./Banner Health (Reiman) Validation of single nuclei sequencing in Alzheimer's disease across multiple cell types	07/01/2022-06/30/2023 \$116,000
Kendall Van Keuren-Jensen (Co-I) W81XWH-23-MOMRP-D (Bamman) DoD/ The Institute for Human and Machine Cognition An integrative 'omics approach towards personalized protein recovery nutrition during multi-stressor operations	09/2023 – 08/2024 \$258,095
Kendall Van Keuren-Jensen (Co-I) NIH/ City of Hope R01 (Chatterjee) Error-Free Genome Editing to Cure Genetic Disease: Mechanism and Application to Rett Syndrome	09/2022 – 05/2027 \$2,880,697
Kendall Van Keuren-Jensen (Co-I) NIH/ University of Arizona R01 (Litshitz) Precision targeting of the rod microglia variant in neurological disease	04/2022 – 03/2027 \$890,446
Kendall Van Keuren-Jensen (Co-I) Canadian Institutes of Health Research/ University of Toronto (Pausova) Metabolomic profiling of brain maturation during adolescence	09/2022 – 08/2025 \$76,364
Kendall Van Keuren-Jensen (Co-I) NIH/ St Joseph's Hospital and Medical Center R21(Sattler) Transcriptomic assessment of pathology in PD with dementia and dementia with Lewy Bodies using iPSC neurons and brain tissue of the same individuals	07/2022 – 06/2024 \$207,630
Kendall Van Keuren-Jensen (Co-I) NIH/Massachusetts General Hospital R01 (Das) Characterization of beta-cell-specific extracellular vesicle cargo as functional biomarkers for type 1 DM disease (TEDDY)	07/2022 – 06/2027 \$974,185
Kendall Van Keuren-Jensen (Co-I) NIH/ University of Arkansas for Medical Sciences R01 (Ferrando) Identifying Intrinsic Predictors of Muscle Dysfunction after Menopause	07/2022 – 06/2027 \$151,920

Kendall Van Keuren-Jensen (Co-I) NIH/ St Joseph's Hospital and Medical Center R01 (Perez) Tau and spliceosome dysregulation in demented and non-demented Down syndrome	07/2022 – 06/2027 \$135,252
Kendall Van Keuren-Jensen (Co-I) Michael J Fox Foundation/NIH/NIA 021821 (Cookson) FOUNDIN- microglial phenotypes from PPMI lines	02/2022 – 01/2023 \$261,074
Kendall Van Keuren-Jensen (Co-I) NIH/ The Institute for Human and Machine Cognition R01(Bamman) Primer Trial: Physiologic Reserve increased via Multimodal Exercise Rehabilitation to Improve Exoskeleton-assisted Walking Performance	09/2022- 08/2027 \$655,246
Kendall Van Keuren-Jensen (Co-I) NIH/ St Joseph's Hospital and Medical Center R21 (Sattler) Mechanisms of A-I RNA editing-mediated nuclear export of TDP-43	12/2022 – 11/2024 \$18,554
Kendall Van Keuren-Jensen (Co-I) NIH/ St Joseph's Hospital and Medical Center R21 (Bakkar) Comparative blood-CSF barrier changes and immune alterations across dementias	04/2022 – 03/2024 \$80,000
Kendall Van Keuren-Jensen (Co-I) WS00479364 (Broderick) Office of Naval Research/ Institute for Human and Machine Cognition Evaluating the Benefits of Intranasal Oxytocin Administration on Human Performance and Metabolism under Extreme Conditions	07/2022 -06/3024 \$681,216
Mark Swanson (PI) Arizona Department of Health Services through the Arizona Biomedical Research Commission A screen for human protein that affect amyloid beta peptide production by gamma secretase	09/01/2022-08/31/2024 \$237,146 Total Project
Matt Huentelman (Co-I) R01 (Bortolato) NIH/University of Utah Disentangling the biological links of violence and alcohol use	04/01/2023 – 03/31/2028 \$118,293
Matt Huentelman (Co-I) NIH/Banner Health R01 (Beach) Neuropathological Consequences and Viral Brain Persistence after SARS-CoV-2 Infection in Consecutive Autopsies from a Longitudinal Clinicopathological Study of Aging and Neurodegenerative Disorder	04/01/2023 – 03/31/2028 \$481,380
Matt Huentelman (Co-I) NIH R21 (Piras) Drug repositioning and pre-clinical screening in Alzheimer's Disease cerebral organoids	04/01/2023 – 03/31/2025 \$528,000

Matt Huentelman (Co-I) Arizona DHS/Banner Health Identification of polygenic risk scores associated with verbal memory performance in non-demented individuals	07/01/2022 – 06/30/2023 \$116,667
Matt Huentelman (Co-I) W81XWH-23-MOMRP-D (Bamman) DoD/ The Institute for Human and Machine Cognition An integrative 'omics approach towards personalized protein recovery nutrition during multi-stressor operations	09/01/2023 – 08/31/2024 \$258,095
Matt Huentelman (Co-I) NIH/Arizona State University R21 (Schaefer) Identifying motor changes associated with AD risk in under-represented minorities using MindCrowd	09/01/2022- 08/31/202 \$446,684
Matt Huentelman (Co-I) NIH R01 (Bamman) Primer Trial: Physiologic Reserve increased via Multimodal Exercise Rehabilitation to Improve Exoskeleton-assisted Walking Performance NIH/Florida Institute for Human and Machine Cognition	09/01/2022-08/31/2027 \$665,246
Matt Huentelman (Co-I) NIH/Rhode Island Hospital OTA (Deoni) Supplement: NEUROLOGICAL SEQUELAE ASSOCIATED WITH POST-ACUTE SARS-COV-2 INFECTION (NEURO-PASC)	04/01/2022-03/30/2023 \$161,337
Matt Huentelman (Co-I) NIH/Northwestern R01 (Rogalski) Asymmetric neurodegeneration and language in primary progressive aphasia	04/01/2022 – 03/31/2027 \$1,972,143
Matt Huentelman (Co-I) NIH/University of Arizona R01 (Grilli) Tracking autobiographical thoughts: a smartphone-based approach to identify cognitive correlates of Alzheimer's disease biomarkers and risk factors in clinically normal older adults.	07/01/2022 – 06/30/2027 \$199,363
Matt Huentelman (Co-I) NSF/University of Arizona (Madhavan) Neural Stem Cell Mechanisms of Resilience across the lifespan	07/01/2022 – 06/30/2026 \$151,309
Matt Huentelman (Co-I) NIH/ City of Hope R01 (Chatterjee) Error-Free Genome Editing to Cure Genetic Disease: Mechanism and Application to Rett Syndrome	04/01/2022 – 08/31/2026 \$2,880,687
Matt Huentelman (Co-I) NIH R03AG073906 (Piras) Genomic determinants of sleep traits as risk and protective factors for Alzheimer's disease	04/01/2022 – 03/31/2024 \$192,000

Matt Huentelman (Co-I) Arizona Alzheimer's Consortium (ADRC)/Arizona State University (Velazquez) Neuronal Rbbp7 as a mediator against tau pathology in Alzheimer's disease	07/01/2022 -06/30/23 \$92,623
Meredith Hay (PI) NIH/NIA R43 AG079647-01 Scale-up Manufacturing and IND Enabling Studies of Extended-Release Formulation of Mas Receptor Agonist for Treating Vascular Cognitive Impairment and Alzheimer's Disease-Related Dementias	2022-2023 \$500,000 Total Project
Meredith Hay (PI) NIA R01 Cerebral blood flow: A target for PNA5 treatment of Alzheimer's disease related dementias (ADRD) and vascular contributions to cognitive impairment and dementia (VCID)	2023-2028 \$10,802 Total Project
Michael Malek-Ahmadi (Co-I) NIH/NIA via ASU R01AG077349 (Schaefer) Using a rapid motor task to enrich clinical trials in Alzheimer's disease requiring amyloid positivity"	09/01/2022-08/30/2027 \$117,877
Michael Malek-Ahmadi (PI) NIH/NIA R03AG077270 Cardiovascular Genotype and APOE ε4 Carrier Status Interaction Effects on Amyloid Load in Pre-Clinical Alzheimer's Disease	04/2022-03/2024 \$174,308
Michael Sierks (PI) NIH FP00029567_Res1 (Sierks) Novel Nanobodies Target Earliest Pathogenic Tau Variants in Neuronal Cells	12/01/2022 - 11/30/2027 \$3,062,553 Total Project
Michael Sierks (PI) NIH FP00032922 (Sierks) Protein variants implicated in disruption of proteostasis in Alzheimer's disease	12/01/2022 - 11/30/2027 \$1,783,179 Total Project
Michael Sierks (PI) NIH via Virtici FP00032400 (Sierks) A Novel Neuron-Penetrating Antibody for the Treatment of Alzheimer's Disease	09/01/2022 - 08/31/2024 \$333,333 Total Project
Michael Sierks (PI) NIH via Virtici FP00033098 (Sierks) A Novel Antibody that Promotes Neuronal Integrity and Neurogenesis for Treating Alzheimer's Disease	09/01/2022 - 08/31/2024 \$231,000 Total Project

Michael Sierks (PI) FP00033636 (Sierks) DOD-ARMY: Army Medical Research Acquisition Activity Targeting TDP-43 Variants as a Therapeutic for Frontotemporal Degeneration	10/01/2022 - 09/30/2024 \$314,000 Total Project
Michael Sierks (PI) FP00033639 (Sierks) DOD-ARMY: Army Medical Research Acquisition Activity A Novel Multiparameter Blood Test for Early Detection and Discrimination of Frontotemporal Dementia	05/01/2023 - 04/30/2027 \$1,504,856 Total Project
Michael Sierks (PI) NIH FP00033781 (Sierks) Disruption of neuronal proteostasis as a tool to identify better therapeutic targets for AD	04/01/2023 - 03/31/2028 \$3,086,459 Total Project
Michael Sierks (Project PI) Arizona Alzheimer's Consortium (AAC) FY23 AAC FY23: Disruption of neuronal proteostasis in early stage Alzheimer's disease	07/01/2022 - 06/30/2023 \$50,000 Individual Project
Nadine Bakkar (PI) NIH/NIA R21 RAG080814A Comparative single cell atlas of blood-brain and blood-CSF barriers in ALS/FTD	12/1/2022-11/30/2024 \$250,000
Nan-kuei Chen (PI) NIH Innovative approaches for enabling robust MRI biomarkers for neurological disorders	4/2023-3/2031 \$350,000 Total Cost
Raffaella Soldi (Co-I) NIH R21 CA280515 (Sharma) Rapamycin-mediated radioprotection as adjuvant in Glioblastoma radiation therapy	04/2023 – 03/2025 \$528,000
Raffaella Soldi (Co-PI) CTR057001 (Sharma/Soldi) Arizona Department of Health Services/ Banner Health A CRISPR knockout negative screen to identify genes that lead to enhancement of efficacy of antibodies targeting amyloid beta (A β) in Alzheimer's disease	07/2022-06/2023 \$116,666
Richard Caselli (Co-I) NIH via ASU (Wang) Improving Randomized Clinical Trial Screening Efficiency and Outcome Sensitivity with Hippocampal Surface Morphometry and Geometric Machine Learning	12/2022-11/2027 \$230,915

Robert Alexander (Co-I) NIH/NIA via IMM (Agadjanyan) Evaluate the Safety, Tolerability, and Immunogenicity of Adjuvanted Preventive Tau Vaccine, AV-1980R/A, in Cognitively Unimpaired APOE ε4 Carriers at the Stage of Preclinical AD	12/2022-11/2027 \$327,926
Sarah Stabenfeldt (Co-I) DOD – ARMY CDMRP (Acharya) Developing vaccines for immunological defense from traumatic brain injury	10/01/2022-09/30/2024 \$300,000
Sarah Stabenfeldt (Co-I) NIH/NIGMS R01 (Stephanopoulos/Sulc) Multivalent protein-DNA nanostructures as synthetic blocking antibodies	12/01/2022-11/30/2027 \$1,316,241
Sarah Stabenfeldt (co-I) NSF Molecular Foundations for Biotechnology (Yan) Design of nanostructures for selective molecular target binding through machine learning	05/01/2023-04/30/2026 \$1,499,308
Sarah Stabenfeldt (PI) NIH/NIA via Phoenix VA R01 (Lifshitz/Stabenfeldt) Molecular tool development to identify, isolate, and interrogate rod microglial	09/01/2022-08/31/2026 \$2,951,028
Stephen Cowen (Co-I) Pending (Melde) University of Florida (sub-NSF) NSF Engineering Research Center for Neural Engineering Systems with Societal Impact (NESSI)	09/2022 – 08/2027 \$5,620,024 Total Cost
Sunil Sharma (Co-I) NIH R44 CA278144 (Kaadige) Development of a potent and selective oral ENPP1 inhibitor for oncology	09/2022 – 08/2024 \$467,258
Sunil Sharma (PI) NIH R21 CA280515 (Sharma) Rapamycin-mediated radioprotection as adjuvant in Glioblastoma radiation therapy	04/2023 – 03/2025 \$528,000
Sunil Sharma (PI) NIH P01 CA269033 (Goel & Von Hoff) A Potent Off-the-Shelf Anti-PSCA Human CAR NK Cell Therapy Directed Against Pancreatic Cancer	07/2023 – 06/2028 \$278,304

Sunil Sharma (PI) CTR057001 (Sharma & Soldi) Arizona Department of Health Services A CRISPR knockout negative screen to identify genes that lead to enhancement of efficacy of antibodies targeting amyloid beta (A β) in Alzheimer's disease	07/2022-06/2023 \$116,666
Sydney Schaefer (MPI) NIH/NIA R01AG077349 (Schaefer and Duff) Using a rapid motor task to enrich clinical trials in Alzheimer's disease requiring amyloid positivity"	09/01/2022-08/30/2027 \$2,482,666 Total Project
Sydney Schaefer (PI) NIH/NIA R21AG077385 (Schaefer) Identifying motor changes associated with AD risk in under-represented minorities using MindCrowd	09/01/2022-08/30/2024 \$440,661 Total Project
Sylvia Eva Perez (PI) NIH/NIA R01AG081286 (Perez/Mufson) Default mode network dysfunction in Down Syndrome	04/01/2023-03/31/2028 \$3,378,346 Total Project
Theodore Trouard (PI) NIH S10 AG072445 3T MRI for Advanced Brain Imaging	2/01/23-1/31/24 \$2,000,000 Total Cost
Thomas Beach DOD via ASU (Sierks) A Novel Multiparameter Blood Test for Early Detection of Frontotemporal Dementia	05/01/2023-04/30/2027 \$139,288 Total Project
Thomas Beach DOD via ASU (Manfredsson) Maladaptive 5-HT raphe-corticolimbic plasticity underlying the development of non-motor behavioral deficits in Parkinson's Disease	04/2022-04/2026 \$111,707 Total Project
Thomas Beach NIH via University of Hawaii R01CA276728 (Wu) Identification of Causal Protein Markers for Pancreatic Cancer Risk by Integrating Multi-Omics Data	12/2022-11/2027 \$47,909 Total Project
Thomas Beach NIH via University of Hawaii R01CA276733 (Wu) Uncovering causal protein markers to characterize prostate cancer etiology and improve risk prediction in Africans and Europeans	12/2022-11/2027 \$38,713 Total Project
Thomas Beach NIH R01 via ASU R01AG080679 (Sierks) Protein variants implicated in disruption of proteostasis in Alzheimer's disease	12/2022-11/2027 \$142,888 Total Project

Thomas Beach NIH R01 via ASU R01AG076705 (Sierks) Novel Nanobodies Target Earliest Pathogenic Tau Variants in Neuronal and Microglial Cells	12/2022-11/2027 \$142,888 Total Project
Thomas Beach NIH via Barrow Neurological Institute R21NS128550-01 (Sattler) Transcriptomic assessment of pathology in PD with dementia and dementia with Lewy Bodies using iPSC neurons and brain tissue of the same individuals	07/2022 – 06/2024 \$31,947 Total Project
Thomas Beach NIH via Rush University R01AG080049 (Romanova) Role of CSF-blood barrier of the meninges in Alzheimer's disease	09/01/22-08/31/27 \$160,846 Total Project
Thomas Beach NIH R01 via ASU (Yu) Effects of Combined Aerobic and Resistance Exercise on Sleep, Cognition, and Blood Biomarkers as Surrogate Endpoints for Cognition in Older Adults with Amnesic Mild Cognitive Impairment	7/1/23 - 06/30/28 \$408,128 Total Project
Thomas Beach NIH via ASU (Nikkah) Elucidating the molecular mechanisms of HFpEF using human heart-on-a chip model	4/1/23-03/31/28 \$161,330 Total Project
Thomas Beach NIH R01 via Stanford University (Boyd) Analysis of whole-body immunological memory	4/1/23-03/31/28 \$1,000,000 Total Project
Thomas Beach NIH R21 via FIU (Gu) ApoE4-Cadmium Interaction in Alzheimer's Disease, with Special Interest in Propionate along the Gut-Brain Axis	4/1/23-03/31/25 \$56,000 Total Project
Thomas Beach NIH R01 Resub via UCSD (Frank) Joint Estimation Diffusion Imaging (JEDI) for Improved Tissue Characterization and Neural Connectivity in Aging and Alzheimer's Disease	4/1/23-03/31/28 \$144,807 Total Project
Thomas Beach NIH R01 SARS CoV-2 (Beach/Serrano) Neuropathological Consequences and Viral Brain Persistence after SARS-CoV-2 Infection in Consecutive Autopsies from a Longitudinal Clinicopathological Study of Aging and Neurodegenerative Disorders	4/1/23-03/31/28 \$6,277,699 Total Project
Thomas Beach NIH R01 via UAB (Chen) Peripheral Biomarkers for Early Diagnosis of Mixed Pathologies in AD/ADRD	5/1/23-04/30/25 \$113,030 Total Project

Wei Zhou (PI) NIH R01 NS131780-01 Understanding the Impact of Carotid Disease and Carotid Intervention in Vascular Dementia	4/1/2023-3/31/2028
Yalin Wang (PI) HHS: National Institutes of Health (NIH) Improving Screening Efficiency and Outcome Sensitivity in Alzheimer's Disease Clinical Trials with Hippocampal Surface Morphometry and Geometric Machine Learning	12/1/2022-11/30/2027 \$3,943,774
Yalin Wang (PI) University of California: San Diego Surface statistics for blind cortical and cerebellar morphometry	4/1/2023-3/31/2028 \$614,177
Yalin Wang (Project PI) Arizona Alzheimer's Consortium (Coon) State of Arizona FY21 Arizona Alzheimer's Disease Consortium	7/1/2022-6/30/2023 \$25,000
Yi Su (Co-I) NIH via ASU (Yu) Effects of Combined Aerobic and Resistance Exercise on Sleep, Cognition, and Blood Biomarkers as Surrogate Endpoints for Cognition in Older Adults with Amnesic Mild Cognitive Impairment	07/2023-06/2028 \$408,128
Yi Su (Co-I) NIH via University of Arizona (Ibrahim) Elucidating the Central Mechanism(s) of Action for Green Light Therapy in Managing Chronic Pain: A Randomized Clinical Trial	04/2023-03/2028 \$1,047,996
Yi Su (Co-I) NIH via ASU (Schaefer) Using a Rapid Motor Task to Enrich Clinical Trials in Alzheimer's Disease Requiring Amyloid Positivity	09/2022-08/2027 \$1,040,000
Yi Su (Co-I) NIH via ASU (Yu) 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	01/2023-12/2027 \$323,272
Yi Su (Co-I) NIH via ASU (Wang) Integrating Deep Learning and Bayesian Networks to Identify Novel Structural Imaging Biomarkers for Normal Aging and Alzheimer's Disease	04/01/2023 – 03/31/2028 \$1,040,000
Yi Su (Project PI) State of Arizona DHA via Arizona Alzheimer's Research Consortium Advanced Imaging and Machine Learning in Alzheimer's Research	07/01/2022 – 06/30/2023 \$250,000

Yi Su (Project PI) State of Arizona DHA via Arizona Alzheimer's Research Consortium Statistical and Neuroimaging Data Science Core Resources Serving the Consortium Members	07/01/2022 – 06/30/2023 \$80,000
Yonas Geda (PI) R01 AG057708 (Geda) NIA via Mayo Clinic and Arizona State University Pathways linking neuropsychiatric symptoms with Alzheimer's disease neuroimaging biomarkers and the outcome of incident Mild Cognitive Impairment/Dementia.	12/2022-12/2027 \$356,362
Yonas Geda (Sub-I) NIA R01 AG059008 (Sabbagh) MCLENA-1: Clinical Trial for the Assessment of Lenalidomide in Amnesic MCI Patients	6/2022-5/2024 \$1,693,093
Yonas Geda (Sub-I) NIH/NIA R01 AG073212 (Sabbagh) Repurposing Sisonimod for Alzheimer's Disease	6/2022 - 7/2026 \$3,762,033.00